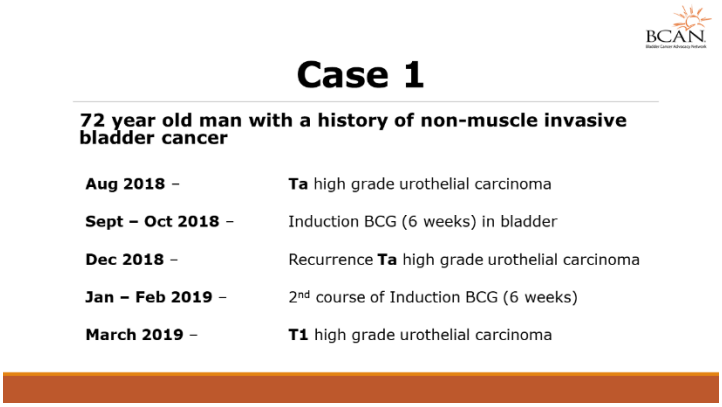
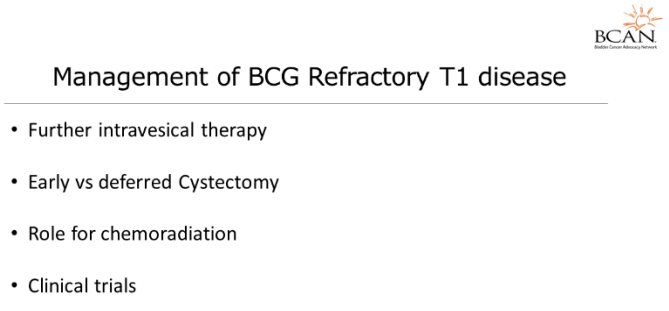
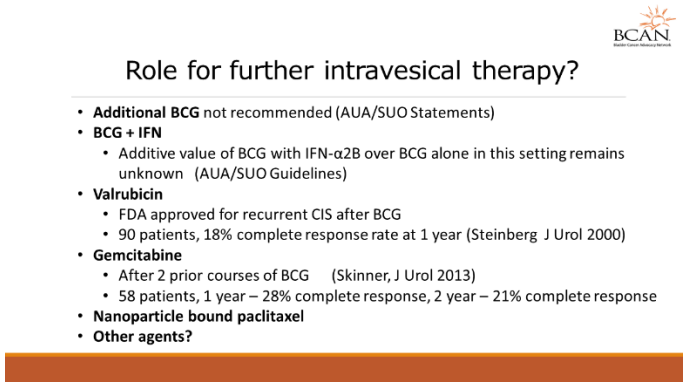
Jonathan Wright: We're going to go ahead and just show you what and how it works. We're going to walk through a couple of cases, present some cases.



This is truly how it works in our conferences. So first case, this is a 72-year old gentleman with a history of non muscle invasive bladder cancer. Last fall had TA high grade urothelial carcinoma of the bladder. Underwent induction BCG, six weeks' worth. Then was found on surveillance cystoscopy to have recurrence of the TA high grade disease.

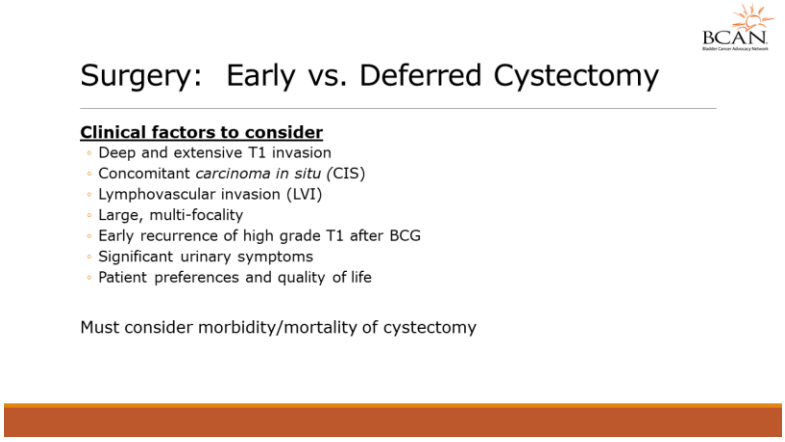
Earlier this year, underwent a second course of induction BCG, six more weeks of BCG therapy in the bladder, and was found unfortunately now to have a progression to T1 high grade urothelial carcinoma. This is a very common scenario that we face and is a challenge to manage. There are different options and not one option is right for everybody? Do we do more intravesical therapy? Do we talk about up front cystectomy at this point? What's the role for chemo radiation and finally clinical trials? There are lots of different intravesical therapy options, but I'll say in this case where someone has failed two consecutive courses of BCG, we would not recommend additional BCG.



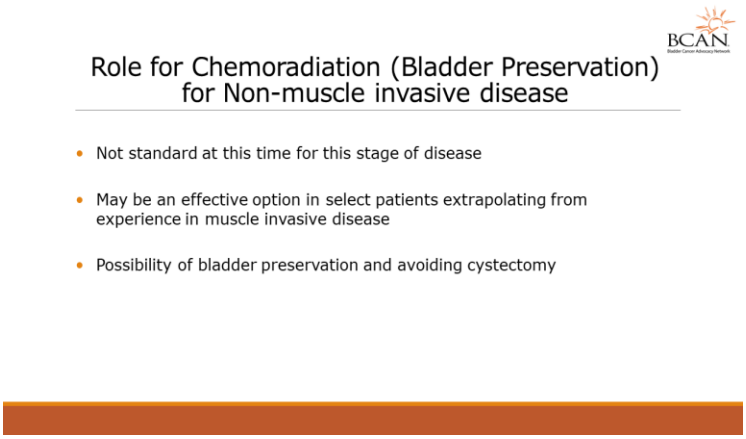


There is talk about adding interferon, although the additional value of adding interferon over BCG alone remains unknown, although there are some data. Valrubicin for patients with CIS has been shown and approved by the FDA. This patient didn't have CIS, so it was just TA to T1 disease. Unfortunately, even with intravesical Valrubicin, the overall complete response rate at one year is quite low. Similarly, another Intravesical chemotherapeutic agent, Gemcitabine, another publication a phase II studies showing that a complete response is low.

Again, there was a subset of patients that will respond, but in the 20-30% range is not where we want to be for most of our patients. Certainly there are other exciting agents that are available. So we often talk in this setting about should we go for a cystectomy in someone that has failed intravesical therapy? Not all patients are candidates for cystectomy for health reasons, or don't want them. We consider a lot of factors about the pathology, about the symptoms, and about the patient goals for deciding for cystectomy because clearly it is a significant operation on patients.



And so, it then begs the question, when we have, and we're faced with this patient, Dr. Liao, what can we, or what could we offer for as far as chemo radiation patients?

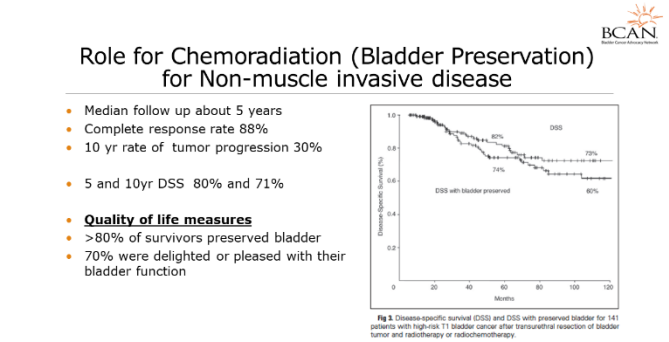


Jay Liao: So typically for earlier stage disease like this, radiation therapy or chemo radiation hasn't had a standard role. So it's not technically standard at this stage of disease, but it holds promise, I think. It may be an effective option when you look in extrapolating from our experience with a little bit more advanced disease where it's actually muscle invasive. There is evidence that you can have successful bladder preservation with the strategy of chemotherapy and radiation therapy. There is a little bit of data though looking at this, and the Europeans have had some track record with this.

One of the largest series comes from the German group. They took 141 patients exactly in this picture that had T1 disease that was either recurrent or high grade, and they were either patients who had decided that they would not undergo cystectomy, or may not have been healthy enough for it. They underwent mostly chemo radiation. Some had just

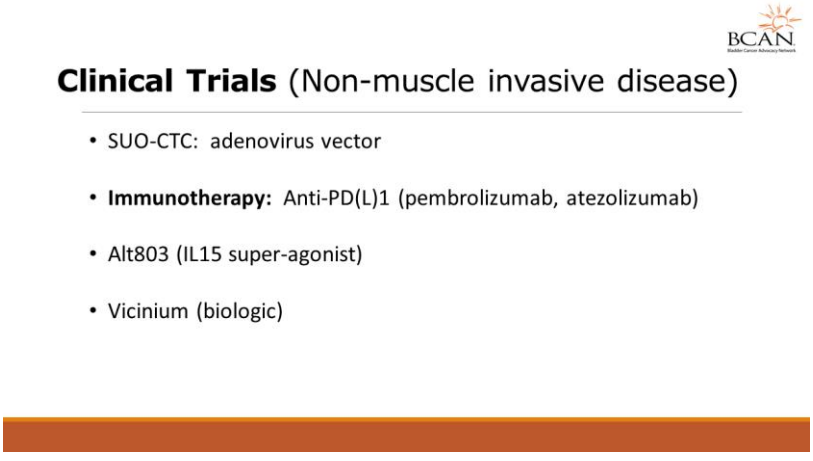
radiation therapy alone. They tracked the patients with follow up for over five years and found there was a pretty high complete response rate with treatment that mirrors our experience in muscle invasive disease if not better. The complete response rate was near 90%.

Ultimately, there were about 30% of patients that had some recurrence later down the road. But this led to a pretty good outcomes as far as cancer survival outcomes were at five years, it was about 80% and 10 years, about 70%, which is close to the outcomes about other strategies. Most rewardingly, there was large proportion of patients that had successful bladder preservation, about 80% of survivors had preserved bladder. Importantly it was a bladder that worked. So the majority of patients were pleased with their overall level of urinary and bladder function.



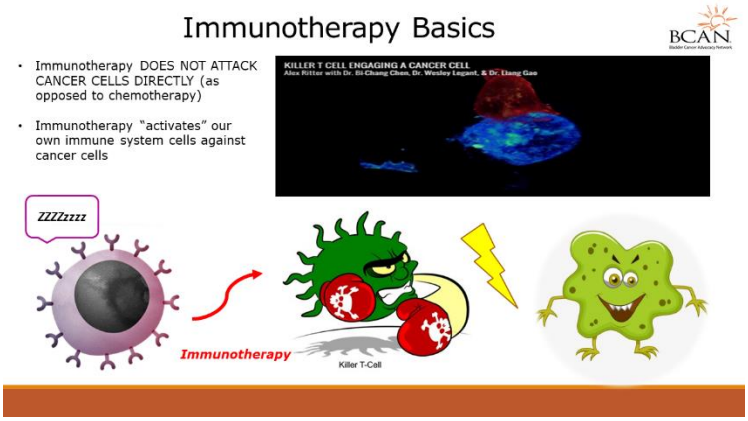
This is something that we're excited about, and we were participants in a cooperative group trial, which is a study that involves multiple hospitals trying to look at a question carefully like this. So this was a small study we briefly had open our institution that was looking at patients that had T1 bladder cancer, often those that BCG didn't work for, and looking at whether this could be a safe alternative to cystectomy. We looked at patients that had a TURBT and then underwent a full dose radiation therapy with concurrent cisplatin chemotherapy. This mirrors the strategy that we use in muscle invasive bladder cancer. Unfortunately, it was a little bit difficult nationally to enroll onto the trial with just the timing of it. But we were able to successfully get one patient onto the trial that I think he's been a long term survivor bladder cancer with successful bladder preservation. So it's something I think we should look into further.

Petros Grivas: So clinical trials are always something we look at and in academic institutions, but even the community there is significant attention about clinical trials because that's how we make progress, how we define new therapy. So definitely we always think clinical trials across a spectrum of disease stages in bladder cancer and other cancers too. Some examples will be shown here in that slide. There is this an important trial from the Society of Urologic Oncology is utilizing an adenovirus vector. There is a study that Dr. Dinney from MD Anderson is leading with instiladrin which interesting therapy trying to stimulate indirectly with immune system in the blood or macro environment that it was.



The result of this trial is still are not reported but the scientific community is looking into this instiladrin trial, to see whether there is any meaningful results in that context. There's definitely trials with immune checkpoint inhibitors. For example, a trial with Interleukin-15, which shows it's a chemical cytokine we

call it, which stimulates the immune system in a very robust way so the immune system can be energetic, activated and try to go after cancer cells inside the bladder. There is also a study looking at the biologic agent called the Vicinium, also the results of that phase, the trial I think are still pending. So definitely significant interest in the research in that context.



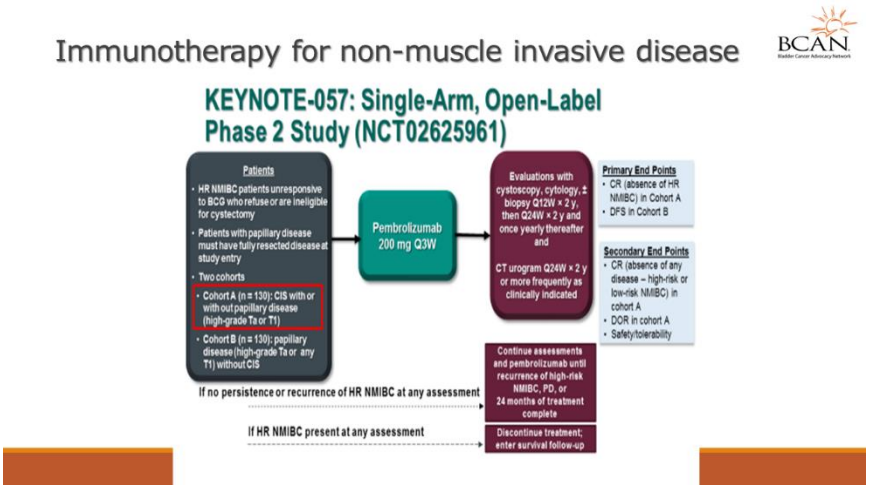
To focus a little bit more on the immunotherapy question, since this attracts a significant attention. There are many questions with recent Nobel prize being given to two individuals who discovered some checkpoints breaks of the immune system. So, the immunotherapy, usually the immune checkpoint inhibitors, work indirectly through activating the immune system. Immunotherapy usually does not attack cancer cells directly as opposed to chemotherapy, but tries to activate the immune system, so the immune system can get energized and go identify, discover and attack cancer cells. Such an indirect way to go after the cancer.

I mentioned a minute ago that two individuals received the Nobel prize a few months ago because they discovered two of the breaks of the checkpoints of the immune system. I always use the analogy of a vehicle when I talk to the patient when I describe these agents. The vehicle has accelerators, gas pedals and brakes, the checkpoint to stop the car to avoid going too fast. The immune system in a similar fashion, it has many gas pedals, many accelerators that stimulate the immune system to go after infectious agents, cancer cells, but also has these checkpoints that are regulatory control molecules that are the breaks of the immune system to avoid any autoimmune reactions. Because if the immune system, our "car" goes too fast, we may have an accident, meaning the immune system attacking our own body, our own self, our own organ. So to avoid this auto immune reaction, we have the check points.

So the cancer cells are tricky because they auto regulate, they try to increase the expression of those breaks at check points of the immune system, so they can evade the immune system surveillance. So, the question here is if you discover those checkpoints, this brakes the immune system, you can potentially block them, so you can see the balance towards the accelerator, the gas pedal, so the car can go faster against the cancer.

This PD-L1 one and PD-1 is one example of two molecules that they come together. PD-L1 can be expressed by cancer cells and PD-1 in the membrane of the lymphocytes, the soldiers of the immune system. The cells that are going after the cancer cells. So when we have an over expression of this PD-L1 checkpoint by the cancer cells, this binds to be the one and "cools down" the immune system, so the cancer cells can try to avoid it. So if we block this interaction, then hopefully we can

stimulate the immune system against the cancer. We have these check point inhibitors that inhibited the PD-L1 or PD-1. One example of that is this molecule called Pembrolizumab, which is the picture in that slide, if you give the drug intravenously once every three weeks, you aim to stimulate the immune system against the cancer. So, this particular clinical trial I'm showing in the slide is an example and there is a similar trial, very similar with Atezolizumab and is being done, and the name of that trial is SWOG 1605. This trial is testing this drug checkpoint inhibitors in patients who had, as Dr, Wright mentioned unresponsive to BCG, recurrent non-muscle invasive bladder cancer. Cohort A, includes patients with carcinoma in situ in the bladder, cohort B, is patient with what we call papillary tumors without carcinoma in situ CIS.



The question here is Pembrolizumab is an alternative option for those patients who either cannot get cystectomy, removal of the bladder or they're too frail to get it or they refuse to do it? Because cystectomy is usually the way to go in this BCG unresponsive scenario. This trial has reported some early results and there is some promising activity with that drug. In about three months' timeframe, about a 4 out of 10 patients had no evidence of cancer. The question is, how long can this result last? And this question of duration of response, how long the results last is an active open question that I think is going to give us an answer down the road, whether this agent may have some alert to get approved for that setting, in that particular question.

It's very, very exciting to put this patient on clinical trial. We have this trial open at the university of Washington. We have several patients who have been enrolled, and we continue actively enrollment of patients in this particular trial. Again, trying to evaluate whether this checkpoint inhibitor Pembrolizumab can have a significant benefit in those patients. When we follow the patients with cystoscopic biopsies, urine cytology and CAT scans to see if there's any activity against the cancer.

Jonathan Wright: So I think, we go through here, we've looked at all the different options for this patient. I think we would agree that in this case, if the patient is willing and healthy, we would recommend as a group a radical cystectomy for this patient. However, if they were not able to or refused, we would then recommend clinical trial most likely. Then if they weren't eligible for a clinical trial, the consideration for other bladder preservation options. Would that be fair guys?

Jay Liao: I agree. I think they are tired of case radical cystectomy, if someone cannot do it, he's too frail or refuses it, clinical trial and then we go to other options such as clinical trials.