



Questions & Answers about Immunotherapy and Bladder Cancer

A Conversation with Dr. Jonathan Rosenberg

Thursday, March 9, 2017

Part III: Clinical Trials in Metastatic Bladder Cancer | No Prior Treatment

Presented by

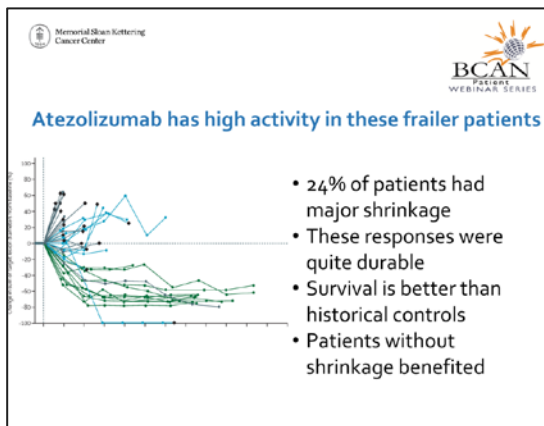
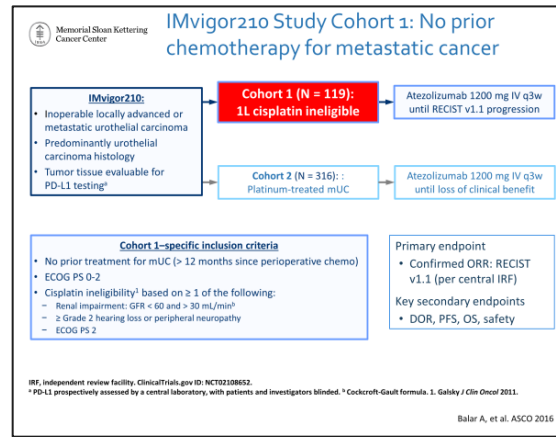


Dr. Jonathan Rosenberg is an Associate Member and Section Head for Non-Prostate Genitourinary Cancers of the Genitourinary Oncology Service at Memorial Sloan Kettering. He's also an Associate Attending Physician at Memorial Hospital at Memorial Sloan Kettering, and he holds the Enno W. Ercklentz, Jr., Endowed Chair. After earning his medical degree from Harvard in Boston, he did his internship and residency in internal medicine at New York Presbyterian Hospital, Cornell, in New York. His research focuses on testing novel therapeutic approaches and correlating novel genetic biomarkers with clinical outcomes in bladder cancer.

Now I'm going to talk about patients who have not received prior treatment for their metastases. These are patients who either presented with metastatic bladder cancer or who had prior treatments, like a bladder removal or kidney removal, and may have had some chemotherapy a while ago, more than a year ago, but then the cancer relapsed and they weren't candidates to get cisplatin. These are people for whom outcomes, unfortunately, are not that good. When we have to use carboplatin, for most patients survival is less than a year, even when it works. While there are some outliers and people who do really, really well, the outcomes are just not so good. We decided as a field that we needed to test these drugs based on how promising they were at least in a subset of patients who previously received chemotherapy. We decided to test them in patients who had not received chemotherapy and couldn't receive the best chemotherapy.

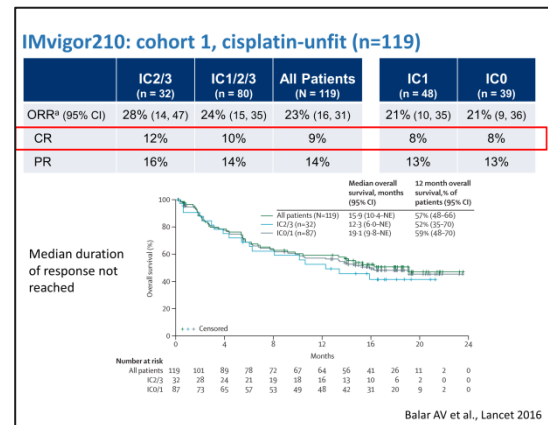
Back to this study, Imvigor210 testing atezolizumab. This is the first cohort, although it actually accrued chronologically second for a variety of reasons. These are patients who are cisplatin ineligible. They couldn't get the best drug for bladder cancer, which is cisplatin. The reasons for that are based on

kidney function, hearing issues, or just general physical status. These are some of the major side effects that cisplatin can cause. It can cause hearing damage. It can cause kidney damage. It can really take the wind out of people's sails, and people who are already having problems with their energy level and their ability to be functional don't tolerate cisplatin at all or tolerate it very poorly, and it tends not to work very well. These patients were the ones who were eligible for this trial. This was a sicker patient population than many of our clinical trials on average.



Atezolizumab was found to have high activity in these frailer patients. About one quarter of patients had major shrinkage of tumors, and these responses were quite durable. The majority of patients, 70 to 80 percent of patients, still were responding if they were responding initially at the time that the data was evaluated. Even if there was not dramatic shrinkage, there were still patients who did derive some benefit at 6 to 12 months. We see here that there was, again, this rapid decline in tumor burden for some patients that seemed to last for a very long time.

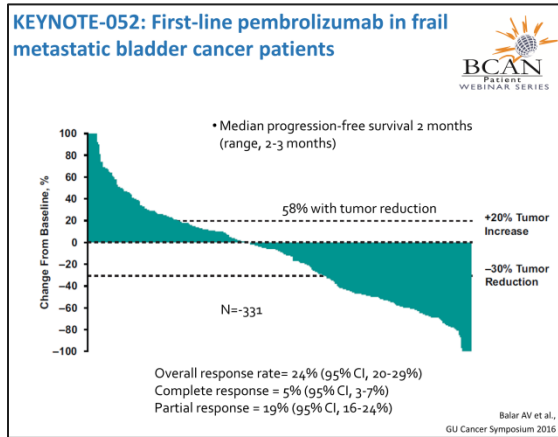
In fact, we see that about 9 percent of patients on this clinical trial have complete disappearance of the visible cancer, which, again, we don't expect to see with treatment like carboplatin, when we're thinking about what are the other options for these patients, and, in fact, the survival of patients, remember I said less than a year on average, here almost 16 months with atezolizumab in this clinical trial. This is about the survival that we see on a lot of the clinical trials with cisplatin chemotherapy. Here we have a group of patients who can't get cisplatin who live as long as the patients who have gotten cisplatin, at least historically, and so this is felt to be a very promising option for patients. I think this is under review with the FDA at this point, and we'll see what their decision is. If they agree, then this drug will be available for patients who can't get cisplatin chemotherapy.



The other trial that looked at this was pembrolizumab. Again, that was the drug that we talked about a few minutes ago where it improved survival in patients who had prior chemotherapy, so they tested this in a very similar patient population. They added an extra category of people who had congestive heart

failure who can't get cisplatin as well, so they tested it in this patient population. Everybody got the same treatment with pembrolizumab, and they looked at the outcomes of things.

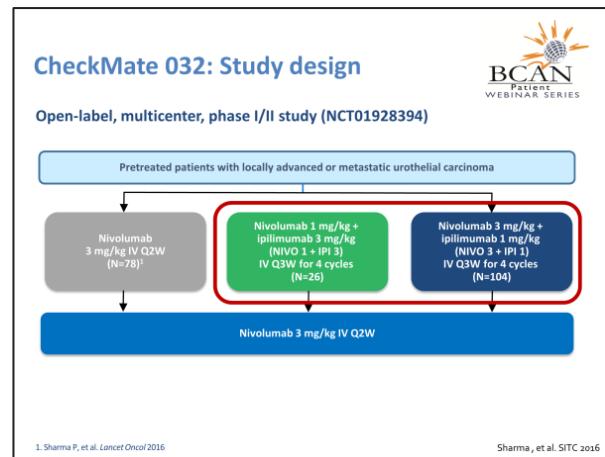
In this trial they found that more than 50 percent, actually 58 percent of patients had some degree of



tumor reduction. About an identical number, 24 percent, had major responses like the atezolizumab study I just told you about, so essentially identical amount of anticancer activity with 5 percent complete responses. It's interesting. This complete response rate may go up over time, because what we've seen happen is that there are patients whose cancers slowly melt away, very slowly. They get major shrinkage and then they get more shrinkage very slowly. I suspect this number is going to go up, but the 24 percent may not get much higher. Again, robust anticancer activity. Very, very exciting.

We see these swimmer's plots again. Each one of these lanes is a patient, and we see that there are many people where you see the arrows who are still on treatment all the way across, and their responses, when they occur, occur by about two months for the majority of patients. There are some people obviously where it stopped working, you see these black dots, but the majority of people they're still trucking, and that's very exciting and very different than what we would expect to see with chemotherapy. In this trial people were quite frail. There were a lot of people who had a lot of medical comorbidities. There were a lot of people who really might not have been candidates for much in the way of cancer treatment. There were many patients in their eighties who went on this trial. These drugs seem to be quite good in elderly patients because of their tolerability.

One last set of clinical trials I want to talk to you about are these immune-immune combinations. The thought is that if we attack more than one place on that cancer immunity cycle that we talked about at the beginning, that we might get either additive or synergistic activity where patient's tumors might be more likely to melt away. There was a study that we participated in here at multiple centers combining a drug called ipilimumab, which is a mouthful to say the least, it's a CTLA-4 inhibitor, with nivolumab, the PD-1 inhibitor, at two different dosing schedules. Then patients went on to continue with nivolumab as single therapy. These regimens were tested in melanoma, and the combination was really, really good, but also really, really toxic. The question is how good is it and is the toxicity worth it?



What we see here is that nivolumab in this trial had a 24 percent response rate, so higher than the other trial that we talked about. When you combine it at this dose level, 3 mg of nivolumab and 1 mg of ipi, the response rate really wasn't different, but if you flipped the dose you got a much higher response rate. But notice there's only 26 patients here, and so this trial is still ongoing and they're recruiting more patients right now to this cohort to see if it really is almost a 40 percent response rate. I would say that the side effect profile is not nearly as good with the combination of therapies. The side effects are manageable, but it's much more common.

I want to take a minute to talk about side effects, because there's a lot of positive press about immunotherapy that sometimes ignore the potential negatives that are out there. The way these medicines work is that they stimulate the immune system and they turn the immune system on most of the time if it works against the cancer, but it also can turn it on against normal cells because we're disrupting one of the mechanisms of homeostasis, of balance in the body, between the immune system and the rest of the body. This autoimmunity is the major toxicity risk. It can attack anything. People ask, "What can it do?" I tell them,

Memorial Sloan Kettering Cancer Center

Side effects of immunotherapy

- These medications stimulate the immune system
- Most likely to attack the cancer cells
- But can attack normal cells
- This leads to autoimmunity-> major toxic risk
- This can attack any organ
 - Intestines, lungs, liver, pancreas, thyroid, brain, nerves, skin, pancreas, adrenal glands, etc
- Can happen quickly, and even within a few weeks of starting treatment
- May be more likely when we combine immune drugs with each other

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"It could do almost anything, but these are the common things." Skin rashes tend to be more common. People often get thyroid problems, which we treat just by giving thyroid hormone. Some of these side effects can happen really fast, even within the first few weeks of treatment. It appears to be more likely when we combine two immune drugs together.

The good news is that most of the side effects are mild. In the atezolizumab study that led to the drug approval, 30 percent of patients had no side effects that could be attributed to the drug, which is pretty profound. We

certainly don't feel that with chemotherapy. About 10 to 15 percent of the time the side effects can be quite severe, unfortunately. The treatments generally involve immunosuppression, turning off the immune response. Corticosteroids are used, like prednisone or other medicines like it, and even more potent immunosuppression is occasionally needed.



What's fascinating to me and other clinicians is that the autoimmunity can be turned off, but the anticancer immunity if it's there often persists and can stay on. So even if you need steroids to manage side effects, it's not a disaster. If the treatment's working, it's likely to continue to work. It is very important to report new symptoms to your doctor, though, and you don't want to let things get serious before you say anything, so I warn patients if they're having any breathing issues or diarrhea, those are signs of potential side effects on the lungs or the intestines, and they can get out of control somewhat quickly. If you get a cold and you're coughing, and you're having some shortness of breath, you've got to let people know because it may not be a cold. It might actually be a side effect. Same thing with loose bowels. If you have one loose bowel movement, all right, not such a big deal, but if you have two, three, four, five in a day, you better get on the phone and talk to your doctor.

Our challenge today as physicians and healthcare professionals who take care of bladder cancer is that while this is a chemotherapy sensitive malignancy and chemotherapy with cisplatin can even cure people, in immunotherapy sensitive malignancy, and I think we're going to see some people cured with immunotherapy, the majority of patients do recur with resistant disease, and we need to do better. We're working hard at identifying new drug targets and new pathways forward. I do think this is a new hope for patients with

advanced bladder cancer. The survival appears to significantly exceed chemotherapy regardless of prior treatments. On average, the side effects are modest, but severe side effects can occur. There is one group of patients which have not been well studied because they've been excluded from trials, and these are people with significant autoimmunity, like inflammatory bowel disease, lupus, and rheumatoid arthritis. In those patients there are special risks around using these medications and it's a more subtle and complicated discussion.


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Finally, I hope that we're going to see that combinations of immune drugs may augment the anticancer activity, but also can have increased side effects, and we have to understand all of this in order to see our way forward for the future.



Immunotherapy in urothelial cancer

- In bladder cancer, survival appears to significantly exceed chemotherapy regardless of prior treatments
- Side effects are generally modest
 - However, severe side effects can occur
- Patients with severe pre-existing autoimmunity may have more risk
 - Inflammatory bowel disease, lupus, rheumatoid arthritis, etc.
- Combinations of immune drugs may augment anti-cancer activity, but also may have increased side effects
- Impact has been transformational in both diseases



Thank You



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Be well

