



Questions & Answers about Immunotherapy and Bladder Cancer

A Conversation with Dr. Jonathan Rosenberg

Thursday, March 9, 2017

Part II: Clinical Trials in Metastatic Bladder Cancer | Prior Treatment

Presented by

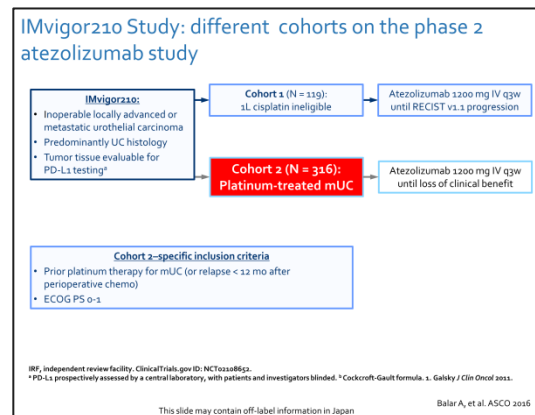


Dr. Jonathan Rosenberg is an Associate Member and Section Head for Non-Prostate Genitourinary Cancers of the Genitourinary Oncology Service at Memorial Sloan Kettering. He's also an Associate Attending Physician at Memorial Hospital at Memorial Sloan Kettering, and he holds the Enno W. Ercklentz, Jr., 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.

We're going to talk a little bit about the clinical trial data, and how that has impacted how we care for patients with metastatic bladder cancer. Atezolizumab was FDA approved last year, and it was actually the first new drug approved for metastatic bladder cancer.

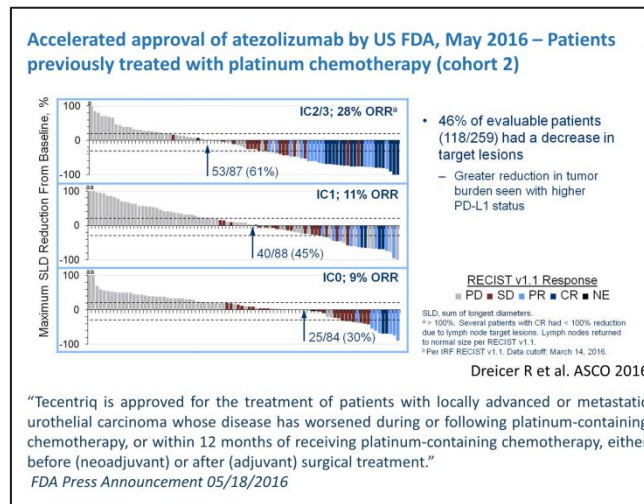
First new treatment approved for metastatic bladder cancer in over 25 years by the FDA. There really had been a void of options and useful medications for patients. The study that showed this was a study called IMvigor210. This involved two cohorts of patients. Everybody who was in the study had metastatic urothelial, not just bladder, but could have renal, pelvis, and ureter and urethral or bladder cancer. There were two cohorts. The first cohort were patients who couldn't get cisplatin and had not had prior chemotherapy for metastases. We'll talk about those later. Just file that away, remember that.



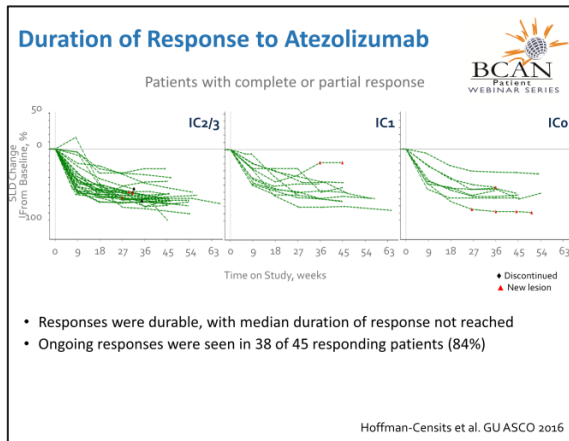
The second cohort, the one in red here, were people who had prior platinum based chemotherapy. These people had had standard treatments and the cancer recurred and was growing despite having had that. The trial did not limit the number of prior treatments that people could have, so there were many, many people, about 40 percent of the trial, had three, four, or five lines of prior therapy, and so this drug was being tested in people who had had a lot of treatment already, which means that perhaps the more treatment you have and the more that doesn't work, the less likely something is going to work in the future. Our expectation was maybe this wouldn't show a lot of anticancer activity, but actually it really kind of did in some ways. This led to the accelerated approval back in May of 2016 for patients who had had previous platinum chemotherapy.

In this trial, these are these waterfall plots again, and they're grouped by something called the immune cell status, IC2/3, IC1, and IC0. One of the things that's been investigated in bladder and other cancers is if the target of the drug, which is PDL-1, is expressed within tumors or on immune cells within tumors, is the treatment more likely to work, because PDL-1 is turned on when there is an immune response that is being suppressed. So if you have PDL-1 that you can see on a stain of the tumor when they look at it under the microscope, that suggests that if you're a patient your immune system might be raring to go but can't, that it's been blocked by PDL-1. You can categorize the staining as high, intermediate, or low, and so we see the three groups of patients here. IC2/3 means high, IC1 is intermediate or medium, and IC0 is low or almost absent.

What we saw was that if you had more staining of PDL-1, the number of patients who had a major shrinking, 28 percent response rate, was higher than if you had little or none. What's interesting is that the responses were there regardless, even if it was less likely to happen. So, this really has colored our perception among all these drugs, that we shouldn't at the moment be testing for PDL-1 staining right now and making decisions based on it, because we really don't know that the person who has IC0, who has low levels of staining, it isn't going to work, because it does work about 10 percent of the time. As we'll talk about a little bit later, the side effects for most patients are pretty mild, so there's no reason to say that we shouldn't think about trying these drugs in a patient who is otherwise a candidate.



This is another way of look at how well these medicines work. These are something called spider plots or spaghetti plots. These are patients who had tumor shrinkage with atezolizumab, and there's other patients where it didn't work. In these patients, we see each patient represents a line, and this is the amount of cancer that they have. Starting at the beginning, everybody is set to zero. Then we look at the change over time. If something grows it goes up, and if something shrinks, it goes down. What we see here is that there are these rapid drops, so at nine weeks the majority of patients who are going to

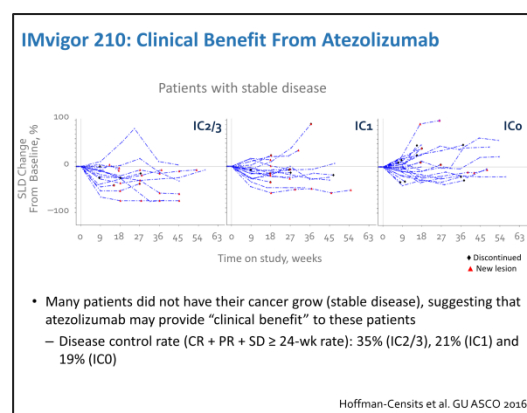


have a response started to have shrinkage and response. What we see is that then the curves start to flatten out, and the amount of cancer is much less, and it's stable and it stays stable. There are a high rate of people, once you get into that category of doing well, they tend to stay doing well for a long time. It's not everyone, obviously there's one patient here where it started to grow, but about 84 percent of patients on the trial if they achieved a response, and that was about 15-16 percent, of those 16 percent 84 percent of them it was longterm. Longterm defined as 2014 to now. Many people are still on treatment.

What we also see is there are fewer people who had these good responses if they have low levels of PDL-1 staining, the IC₀ group. There are more people who are more likely to have a response if they have IC_{2/3} tumors than if they have IC₀, low expression, but the durability and the quality of those responses are no different, which also leads us to say I wouldn't withhold treatment for someone who had this value because even though it's a small number of people where it works, those patients seem to do quite well.

Also, there are a lot of patients who don't have major shrinkage, but don't have tremendous growth of their cancer, the so-called stable disease patients. These patients, many of them will last quite a long time, and you'll see that over time the cancer's not growing. Because this is a relatively non-toxic treatment, this is something that's, I think, a good thing. People feel reasonably well, the cancer's not growing, they're getting some benefit. There is a higher proportion of patients who have this so-called clinical benefit rate, where they have essentially cancer that's not bothering them so much and they can live their lives, which is really what you want out of a treatment.

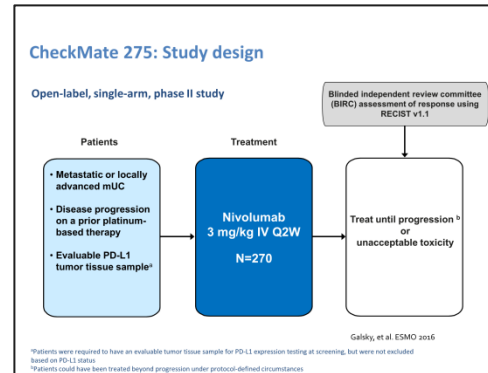
We do see that we do have more work to do here. The average survival in this study was only about eight months, but what we do see also is that the curves probably are flattening out as time goes on. This is the percentage of patients who are alive at any given time, and what we're seeing, and I think this is going to continue over time, that there is going to be, and I don't know what percentage it's going to be, but 20 to 30 percent of patients may have longterm stability of their cancer, and hopefully a good quality of life. We obviously need to get the curve up to here, but this is certainly better than what we've had before.



Very recently, in fact just last month, we've had a second drug approved for advanced bladder cancer. This is nivolumab. Nivolumab is one of the PD-1 inhibitors. It binds PD-1. It's an antibody. It's

administered every two weeks while atezolizumab is administered every three weeks. The study that led to its approval is CheckMate 275.

This study was another single-arm study. It didn't have two cohorts. It only had one cohort. In this study, everybody got the drug, everybody got nivolumab as a set dose based on their weight, and they were treated as long as it seemed to be working or unless they had some really bad side effects. There were about 270 patients enrolled on this trial. What they found was not all that different than the other drug atezolizumab, that the response rate, the proportion of patients, the percentage of patients with major shrinkage was 19.6 percent, just shy of 20 percent.



They also found, similar to the other drug, that there were some patients who had complete regression, complete disappearance of their cancer, which is something we really don't see in patients who have had prior platinum chemotherapy. This number is usually zero in any of the trials we have done historically. There are patients who do extraordinarily well, and when they looked at their PDL-1 test, which is a different antibody than the one we were talking about before for testing the tissue to see if their PDL-1 is expressed in the tumor, they found that, yes, they also saw higher levels of responses, and

Antitumor activity of nivolumab

- PD-L1 measured on tumor cells
- Median follow-up was 7 months (minimum of 6 months)

Outcome, %	All N=265 ^b	PD-L1 <1% n=143	PD-L1 ≥1% n=122	PD-L1 ≥5% n=81
Confirmed ORR by BIRC*	19.6	16.1	23.8	28.4
95% CI	15.0–24.9	10.5–23.1	16.5–32.3	18.9–39.5
Best overall response				
Complete response	2.3	<1	4.1	4.9
Partial response	17.4	15.4	19.7	23.5
Stable disease	22.6	17.5	28.7	28.4
Progressive disease	39.2	46.9	30.3	25.9
Unable to determine	18.5	19.6	17.2	17.3

^aBy RECIST v1.1. ^b96% of 270 patients were evaluated for efficacy, as 5 patients had insufficient follow-up.

- Confirmed ORR in patients with PD-L1 <5% was 15.8% (95% CI, 10.8–21.8)

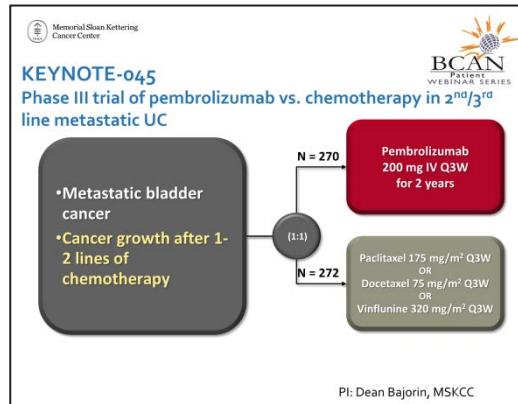
Galsky et al. ESMO 2016

that although for them if the PDL-1 level was low, the response rate was 16 percent, but if the PDL-1 level was high, the response rate was 28 percent. To me, this also says, again, we should not be testing people, because the drug, even though it may be less likely to work, can work very well and can be somewhat durable in these patients, even if there isn't a lot of PDL-1 testing. A lot of people are very focused on knowing their PDL-1 status now I find, but I actually find it confuses the situation currently. That could change in the future as we get different drugs and maybe more drugs and even better drugs.

Here again we see that in patients who for the entire population the survival was around 8-1/2 months. We see perhaps there's starting to maybe be some flattening on the curve, and that people who had higher levels of PDL-1, survival seemed to be longer. Again, percentage of patients who are alive over time generates these curves. None of these have been a home run, but I they've been, I would say, a double compared to wherever we've been before and will give us a good platform to start building upon.

This bring us to the third drug which has been studied in a large clinical trial, and this is pembrolizumab. It's a PD-1 inhibitor as well. It's another antibody targeting PD-1. Both nivolumab and pembrolizumab

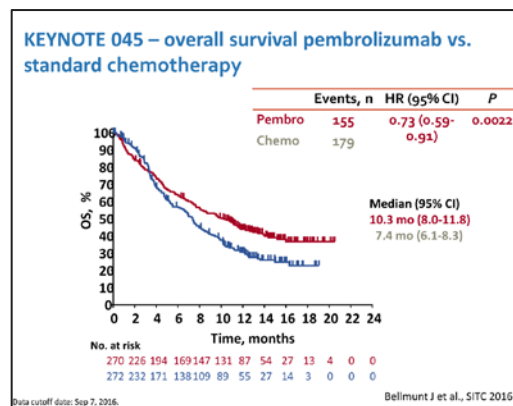
are also approved in melanoma and lung cancer, and atezolizumab, the first drug we talked about, is also approved in lung cancer. Pembrolizumab was tested in a randomized phase 3 clinical trial compared to chemotherapy in patients who had prior chemotherapy with platinum drugs. This was in chemotherapy-resistant cancer. This was the first time ever that we've seen a drug lengthen survival. This was a landmark study in advanced bladder cancer.



This trial accrued a very similar patient population, although they did limit it to one or two prior chemotherapies, whereas the other studies didn't have that restriction. Patients were randomized, randomly allocated to either get pembrolizumab or get chemotherapy, and the chemotherapy was at the discretion of the doctor taking care of the patient. These were the drugs that we had been using previously. Two of them are taxanes, one is docetaxel, which is Taxotere, the other is paclitaxel or Taxol, and this other drug, vinflunine, which was used in Europe, but is not available here in the

United States. Patients were randomized to either chemotherapy or immunotherapy, and about 270 patients were on each arm.

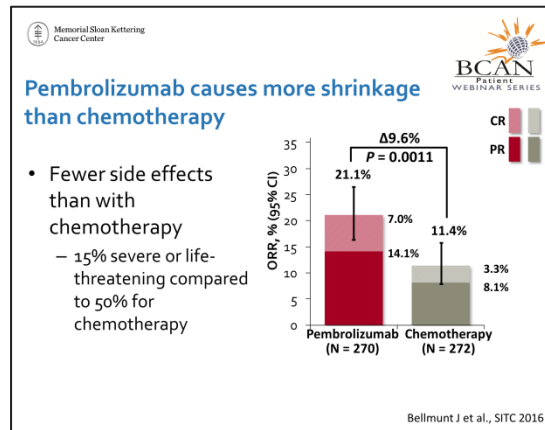
What this study showed was that compared ... The blue line are patients treated with chemotherapy, and the red line is patients treated in with immunotherapy. While the data is still somewhat immature, each one of these little hash marks means that there is a patient who is still getting treated or alive, and there's a lot of hash marks, meaning there are a lot of people still being followed. The curves split. The patients who were on immunotherapy do better. We see again this flattening out of the curve, which suggests that perhaps over time we're going to see a proportion of patients who do very well over the longterm. The averages, again, are not spectacular, 10.3 versus 7.4 months, but they sort of belie the fact that there's a whole mess of patients who are doing quite well who wouldn't have done well with chemotherapy.



We hope this will lead to the drug being FDA approved in the next six months or so. It strikes me that this is almost a certainty unless there's something we don't know about. What is very interesting, though, is that the curves cross at about four months, and there are some patients where immunotherapy doesn't really work very well for them at all and they die relatively quickly, while chemotherapy can kind of keep a lid on things for a little while, but then it starts to fail over time. There may be some patients who might be better off getting chemotherapy, and there may be some patients ... Maybe we should be thinking, from a research point of view, maybe we should be combining with

chemotherapy so that we help more people, because there are clearly some people where treatment doesn't work well for them at all.

At one year about 43 percent of patients are alive compared to 30 percent with chemotherapy. Again, it's a modest difference but a real difference, certainly if you're in that 13 percent. We don't know who

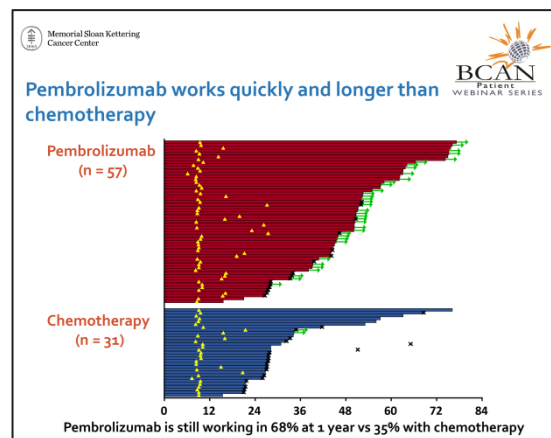


they are in advance, but I hope everybody will be in that group. The patients who experience responses, again we find that they tend to be quite durable. They also saw that pembrolizumab caused more shrinkage than chemotherapy. There were almost twice as many patients who had shrinkage with pembrolizumab, 21 percent versus 11 percent. Fascinating and exciting to see was that there were 7 percent of patients who had what we call complete responses, complete disappearance of all cancer. This was not something that we've seen before in the treatment of bladder cancer,

and it represents a new thing for us as bladder cancer doctors, and it's very good. No one is quite sure how long to treat these patients. If you're doing very well and you've been on treatment for a couple of years and there's no cancer left, do you stay on treatment or do you come off?

There were much fewer severe or life-threatening complications on the immunotherapy arm of the trial, about 15 percent compared to about 50 percent for chemotherapy in this trial. This is the number that I usually have cited for patients historically, so it was good to see that this number was similar in this trial. Immunotherapy on average appears less toxic than chemotherapy in this patient population. Quality of life tends to be better and side effects tend to be fewer.

One other thing that's very interesting is that pembrolizumab and all the other drugs, when they work, they work quickly. These figures are what we call swimmer's plots. Each one of these lanes is an individual patient, and each one of these little triangles represents the time when the cancer passed the threshold to be called a response. We see here that it's at about 8 to 10 weeks that patients, regardless of what they got, the responses happened very quickly. Tumor reductions occur fast on average. We also see that there's a sprinkling of people where it takes longer and the tumor shrinkage is slower, but at the end of the day there's still a lot more people on treatment with immunotherapy who have the red bars with the green arrows, compared to just a few people still on chemotherapy with the blue bars down here, showing the significant durability and tolerability of immunotherapy in this patient population.



My guess is we're going to see as time goes on the other clinical trials that are ongoing that are comparing immunotherapy to chemotherapy are going to show very similar effects. In fact, 68 percent of patients at one year who were treated with pembrolizumab, it's still working for them, compared to just 35 percent with chemotherapy. Based on these three clinical trials, immune therapy has become the new standard of care for patients who have had prior platinum chemotherapy. This drug, again, I expect will be FDA approved within the year. I'm not sure any one is better than the other, which I'm sure may be a question people have, which one should I get? There aren't significant differences that we can tell between them, but they've never been compared against each other anywhere in any cancer, and so we don't have an answer to is atezolizumab different than pembrolizumab different than nivolumab.

