BCAN Patient WEBINAR SERIES

Clinical Trials: Advanced or Metastatic Bladder Cancer

Wednesday June 22nd, 2016

Part III: Question and Answer

Questions Answered by

***Andrea Apolo, MD** is a Lasker Clinical Research Scholar and tenure-track investigator and Chief of the Bladder Cancer Section of the Genitourinary Malignancies Branch of the National Cancer Institute. She received her MD from Albert Einstein College of Medicine in New York, and completed an internal medicine residency at New York-Presbyterian/Weill Cornell Medical Center. She followed up by a medical oncology fellowship at Memorial Sloan Kettering Cancer Center, and then joined the medical oncology branch at the NCI, with the charge of developing a bladder cancer translational program. She holds board certifications for internal and medical oncology.*

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.

Moderator: What I'd like to do at this point is open up to some questions from participants on this webinar, and so I'm going to ask the first question would be, **should individuals with metastatic bladder cancer have a genetic analysis before deciding on a treatment plan or a clinical trial? What is your opinion on that?**

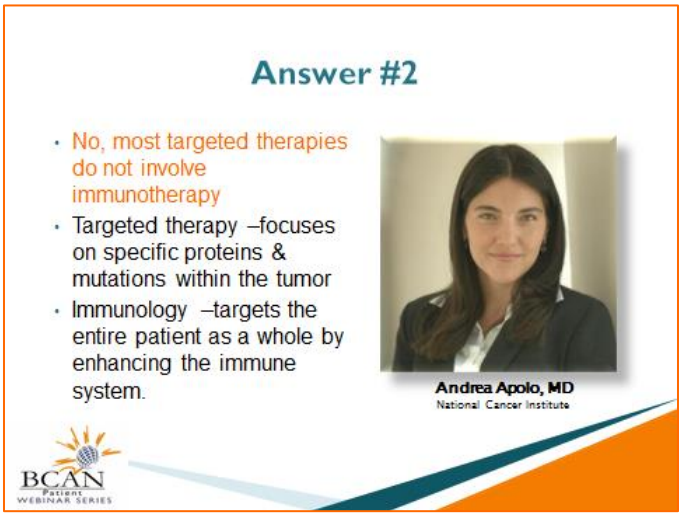
Dr. Besty Plimack: I think Andrea and I are going to agree on this, but genomics are evolving so fast that having up-to-date information and using state-of-the-art analysis techniques, we think will ultimately benefit our patients. Now, whether that should be done and we should wait for the answer from one of these tests before selecting something is a more difficult choice. I think getting the test done if you have metastatic disease will ultimately poise us to be in a good position to then select therapy down the road, but in my clinics, often, we send the test and then we talk about what we have available immediately and then we sort of use the results later on to help inform our decision making. Andrea, I don't know if you ...

Dr. Andrea Apolo: I agree. I think it's helpful in a lot of ways because it tells me a little bit about the biology of the tumor as to some mutations tend to be more aggressive than others. Some mutations tend to make the tumors more susceptible to certain therapies than others, but do we have a standard in bladder cancer, and we don't yet. In terms of "we have a mutation, we're going to treat you with this therapy", we don't have that, but it definitely opens up avenues for enrolling the patient in a phase 1 clinical trial where they're testing drugs that may target that mutation. It opens up treatment possibilities for future trials, like Dr. Plimack mentioned, but not really do we have anything that's commercially available.

I get, sometimes, these reports from certain laboratories where they've analyzed the tumors and they're giving treatment recommendations and those are not approved yet for that specific patient population, so I'm really surprised they would go as far as doing that. I think there's a lot of value into profiling the tumor and kind of understanding a little bit more about how aggressive it is and what mutations it carries. In clinical practice we're not using it yet to give standard therapies. We're actually using it to potentially enroll somebody in a clinical trial that may test these mutations, that may target these mutations.

Moderator: This might be a good follow-up question relating to that. **Do most targeted therapies involve immunotherapy of some kind?**

Dr. Andrea Apolo: No, most targeted therapies don't involve immunotherapy. It's actually, targeted therapy is the opposite of immunotherapy, in a way, because targeted therapies are targeting specific proteins or mutations within that tumor and immunotherapy is not targeting, it's not targeted therapy. It's the opposite. It's actually globally targeting the patient. It's really, it's enhancing the immune system to recognize the tumor as foreign, not any specific mutation.

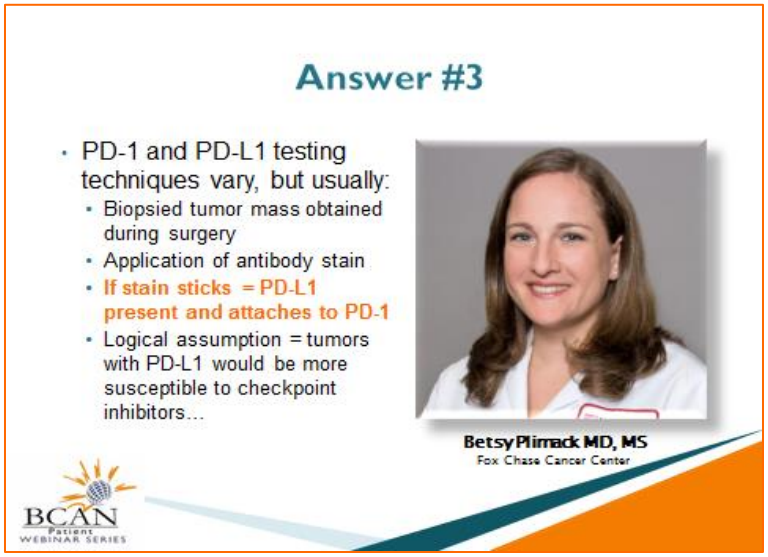


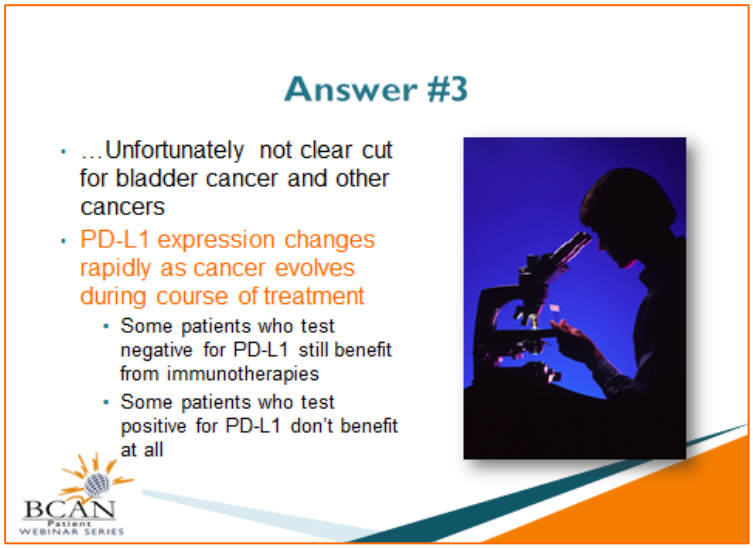
Although, there has been some research into finding biomarkers for patients that are responding to the checkpoint inhibitors versus the ones that aren't, and PD-L1 expression on the tumors or on the immune cells have seemed to be an early marker, not yet established for critical use, but an early marker that some patients that have the expression of this biomarker on the tumor may have more susceptibility to immunotherapy. There's a lot of research right now, ongoing, to see in the patients that don't have these proteins on the surface of their tumors or on their immune cells, can we induce these proteins by, either different immunotherapies, or by chemotherapy, or targeted therapies.

Immunotherapy and targeted therapies are not the same. They're different and that's why combination therapy, in a way, makes sense, because you're taking two different mechanisms of attacking the tumor and using them together.

Moderator: **How do you know if the tumor has PD-1 binding? Is it tested in all metastatic cancers or just certain ones?**

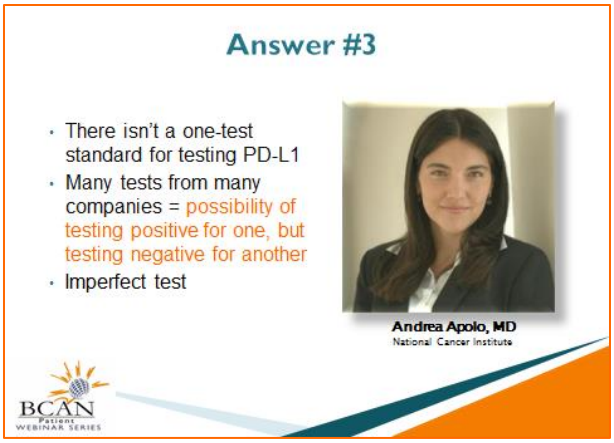
Dr. Betsy Plimack: PD-1 testing or PD-L1 testing is something that there's been a lot of research into. There are a lot of different ways to test for it, but most of them involve taking a piece of a patient's tumor, often obtained at the time of surgery, or sometimes taken as a biopsy from a metastatic site, and then applying an antibody stain and looking to see if that stain sticks. If it sticks, that means there's PD-L1 there and that's the ligand that PD-1 latches onto. It stands to be logical to expect that the tumors expressing PD-L1 would be the ones that would be most susceptible to PD-L1 inhibition with the checkpoint inhibitors.





Actually, as it turns out, in bladder cancer and in other tumors, it's really not that clear cut. Part of that is because the expression of PD-L1 changes pretty rapidly as cancers evolve and throughout the course of treatment. We do find that plenty of patients who are negative for this test still maintain benefits when they're treated with immunotherapies and the reverse is, unfortunately, also true, patients with very high PD-1 test staining sometimes don't benefit. While there may be a higher proportion of patients who do well with immunotherapy who have that staining marker noted on their tumor, it's just not specific enough, in my opinion, to really use to decide whether or not to try an immunotherapy.

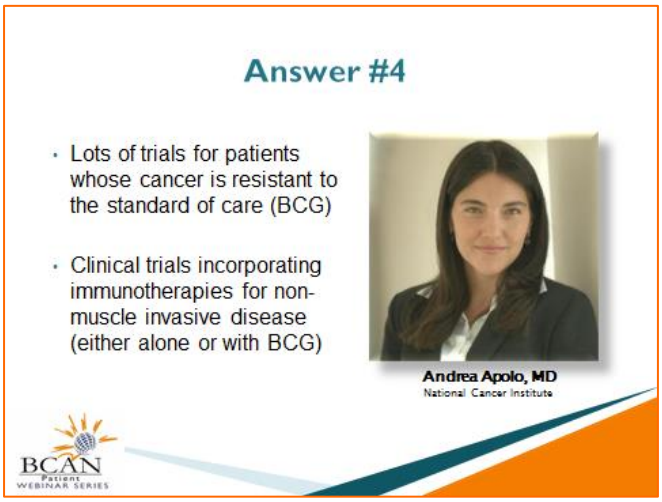
Dr. Andrea Apolo: I agree with that and I think one of all the problems is that there isn't one test for testing PD-L1. Every company has developed their own test and they haven't really been compared to see whether, if you're positive through one test, does that mean that you're going to be positive through another test? We need to standardize the PD-L1 testing in order to get a little bit more information as to what the positivity and the negativity means.



Dr. Andrea Apolo: I agree with Dr. Plimack, the cancer and even your body is very dynamic, depending on kind of, are you sick right now? What's going on? Are you getting chemotherapy? The expression of the PD-L1 in your tumors and in your immune cells can change. When we take tissue from when you had your surgery, which may have been years ago, it may not really represent what is going on in your tumor right now. It's an imperfect test because of we don't have a standardization and because it can change.

Moderator: Great. I think we have time for maybe two more questions. Here is one**: Are there any new treatments for carcinoma in situ of the bladder that you know of? New treatments, perhaps, or new trials that you might know of?**

Dr. Andrea Apolo: Yes, so there's a lot of trials that are currently being developed right now for patients that are resistant to the standard of care, which is BCG therapy given by the urologist. They're actually trying to incorporate, like Dr. Plimack had shown in her slide, incorporate these immunotherapies early on in patients with non-muscle-invasive disease, carcinoma in situ, and giving them immunotherapy, either alone or in combination with BCG, to see if these agents have activity in earlier disease states. There's a lot of research effort ongoing right now for carcinoma in situ.



Moderator: Great. Then, another, final question: **Do international trials help get a drug approved by the FDA or does that research only have to be done in America?**

Dr. Betsy Plimack: That's a great question. We look at trials from all over and all of the available data and the FDA certainly does as well when looking to approve a trial. It is important for clinical trials to enroll patients, usually both in the United States and abroad, so that the tests sort of have brought applicability across those countries, but absolutely the United States FDA takes into account trials done in Europe or other countries and vice versa. The European agencies will look to trials done both in Europe and in the United States when they're looking to approve drugs.

Moderator: This has been an excellent program and I, again, want to just stress that we would have no treatments at all if there weren't clinical trials. No treatments that were safe and effective and I think that this is a really important thing to consider as a patient. **Did you have any closing words that you might want to share, either of you?**

Dr. Betsy Plimack: I just want to thank everyone on the call and out there who has participated in or considered a clinical trial because these advances would absolutely not happen without our brave patients who courageously enroll in these and while we hope each clinical trial that we offer to a patient helps that patient, we know that there's a chance that it won't and so thank you to everyone who's participated in one.

Dr. Andrea Apolo: I agree with Dr. Plimack. I think patients are altruistic to participate in clinical trials and a lot of patients tell me, "This may not benefit me, but if it benefits patients like me or that have what I have then, at least that makes me feel good." Those are beautiful words coming from patients. It's just a really exciting time right now in research and in bladder cancer research. When I started off, 10 years ago, we really didn't have any exciting trials in bladder cancer. We had a lot of things we were looking at and we thought were exciting, but did not pan out and they were failure after failure after failure and the fact that we have now, some drugs that are shrinking the tumor, that are working, and that we can combine these and make things better is a really exciting time to be in bladder cancer research and for patients to participate in clinical trials.