Highlights from the 17th Annual IASLC World Conference on Lung Cancer: International Focus on Emerging Advances in NSCLC Management

Narrator:
Welcome to Project Oncology on ReachMD and the Prova Education Activity: Highlights from the 17th Annual IASLC World Conference on Lung Cancer, International Focus on Emerging Advances in NSCLC Management.

Your host is Dr. Jennifer Caudle. Dr. Caudle will speak with Dr. Edward Garon, who is an Assistant Professor of Medicine, Hematology and Oncology and Director of the Thoracic Oncology Program at the David Geffen School of Medicine at UCLA in Santa Monica, California. Dr. Garon receives research grants from AstraZeneca, Bristol-Myers Squib, Boehringer Ingelheim, Genentech, Eli Lilly, Maruti Pharma, Merck, Novartis, and Pfizer.
Dr. Caudle:
Based on CDC data, lung cancer represents 13% of all cancers diagnosed worldwide and 19% of all cancer deaths, and with almost 225 cases and more than 158,000 deaths anticipated in 2016 in the United States alone, lung cancer is the leading cause of cancer-associated mortality. Non-small cell lung cancer represents approximately 85% of those cases, which makes the need to better identify and treat this disease a critical need.

This is Project Oncology, and I am Dr. Jennifer Caudle. My guest, Dr. Edward Garon, will review data on non-small cell lung cancer presented at this year's World Conference on Lung Cancer in Vienna, Austria.

Dr. Garon, welcome to the program.

Dr. Garon:
Thank you very much.

Dr. Caudle:
To start off our discussion, biomarkers are continuing to be sought in identifying patients who might best respond to agents targeting checkpoint inhibition. What new data has been presented at the conference concerning who should be tested for PD-L1 and when?

Dr. Garon:
So, perhaps, testing for PD-L1 has been over the last year and a half one of the most controversial areas in lung cancer treatment. As you know, the original approval for nivolumab did not include a requirement for biomarker testing. The original approval for pembrolizumab did require biomarker testing. And now, in addition to those two agents, we now have the PD-L1 inhibitor atezolizumab that is approved, and that also does not have a requirement for biomarker testing. However, those are all in previously treated patients. In the frontline setting, there is only one dataset that has been positive, and that is pembrolizumab in patients who have staining at, at least the 50% cutpoint, so at least half of those cells have staining for PD-L1.

In a practical sense, this was sort of the first major meeting after that data was presented, so the first major meeting at which standard frontline PD-L1 testing was considered part of our treatment approach. The approaches that are looking to improve on that, there have been several, and some data was presented both in sessions as well as poster sessions looking at multiple other biomarkers that people have looked at such as mutational load. That was looked at in lung cancer originally in a paper by Naiyer Nizvi that was published in Science showing that the non-synonymous mutational
burden is correlated with response to, in that case, pembrolizumab. Foundation Medicine has also made efforts in this area. There was also some updated data looking at atezolizumab. Their test is somewhat different in that they have looked at both the tumor cell staining as well as the immune-infiltrating cells. Although, at this meeting I would say that we still do not have data that indicates whether or not there is an additional contribution of immune-infiltrating cells. There are other biomarkers that certainly people looked at besides PD-L1 expression and mutational load, things like gene expression, immune cell infiltrate, not the PD-L1 expression but actually the number of immune cells. Although, at this point, I would say those are still fairly early and not the sort of things that are going to be applied in any sort of clinical setting right now.

Dr. Caudle:
More and more patients are being considered for use of immune agents targeting checkpoint inhibition. Are there any groups in who you are particularly reluctant to use immunotherapy? And what about those patients who had a history of autoimmune disease with prior immunotherapy?

Dr. Garon:
There are essentially a few questions that are here. So, one is: What is the role of PD-1 or PD-L1 inhibitors in patients with autoimmune diseases, for instance? And on some level it's very hard to know because, of course, the data that we received regarding treatment decisions is generally based on clinical trial data, and these trials generally excluded patients who were involved in clinical trials. There is now, I would say, sufficient data to state that if a patient were to receive these agents, that they are likely to lose, for instance, a transplant. That is something that people have looked at. People still in some situations clinically will consider that if the transplant is, for instance, a kidney, but for organs for which there is no practical replacement, that, I think, is clearly essentially an absolute contraindication.

On the other hand, in the field we're going to continue to grapple with what to do with patients who have autoimmune disease. And like all of our decisions in medicine, it is becoming clear that this is going to be a risk/benefit analysis and something where one has to gauge the severity and likelihood of worsening of the autoimmune disease in the context of a patient who is dying of Stage IV non-small cell lung cancer.

The additional question is what to do in patients who have had autoimmune sequelae of their prior therapy, for instance, with a PD-1 or PD-L1 inhibitor. Now, of course, not all autoimmune sequelae are equal. Hypothyroidism, which is really the most common autoimmune toxicity that we see, is very easily dealt with with oral pills, and that's generally what we have done. There has been tremendous reluctance in patients, for instance, who have had pneumonitis to reinstitute that. We have very little data to date because not a lot of people have published on rechallenging patients who had severe
pneumonitis. Although, anecdotally, when it is discussed the concern is that many of these patients do then go on to have the same issue recur again.

Dr. Caudle:  
When assessing the response of agents targeting checkpoint inhibition in non-small cell lung cancer, what are the difficulties when interpreting radiographs when using immunotherapies, and has anything new emerged? 

Dr. Garon: 
So, there was not much at this most recent conference that was addressing radiographs. Now, that may be that the conference occurred right on the heels of the RSNA Conference in Chicago, which is the main radiology conference, where these sorts of topics certainly were dealt with. However, in my opinion, the questions about the radiographic analysis of patients with lung cancer, at least to date, has been really much ado about nothing. I think that this is a place where as scientists and clinical investigators we really need to push back and educate. I think that based on some responses that were clearly delayed with immune checkpoint inhibitors in melanoma, it has led to a belief amongst many that the responses to these agents is quite delayed and that, in fact, one would need to, for instance, treat a patient for many months to, in fact, rule out the potential for benefit. 

The FDA has looked back on, for instance, the nivolumab dataset, and individual investigators have also looked back, and in general they are not that frequently when you see someone who clearly gets worse and then does get better. There are some instances where, for instance, scans generally look good in a patient who’s doing well but that there is a new lesion. There are such instances, and in those instances I think practitioners left to their own without a lot of guidance would be inclined to continue those patients on the checkpoint inhibitor, which I think is reasonable. 

On the other hand, I think that for practitioners who have treated lots of people with these agents, I think you will essentially get uniform thought that if you have scans at about two months or later in a patient and the scans are clearly worse and the patient is dramatically worse, that that patient is not likely to benefit from an immune checkpoint inhibitor, at least with the currently available immune checkpoint inhibitors, and that it makes sense to explore other treatment options. 

Dr. Caudle:  
Have any discussions come to light at the meeting concerning adding PD-1 or PD-L1 inhibitors to chemotherapy outside of the context of a clinical trial, and if so, under what circumstances? 

Dr. Garon: 
Sure. So, at the meeting, of course, data from clinical trials is what is presented, and the main trial data
that was presented was presented by Dr. Corey Langer. There is also now an article in Lancet Oncology looking at the KEYNOTE-021 cohort G. So, what I will say, and this is diverging a little bit from the question, but this is one of several datasets that now has sort of been multiply presented, and I will say that I do have some concerns when this happens. Typically, we have had one presentation of data, and practitioners, excuse me, have incorporated that data. On the other hand, for casual observers it may appear that there is a groundswell of data supporting adding a PD-1 or PD-L1 inhibitor to chemotherapy when, in fact, the reality is that it is really the same patients being presented multiple times, and so the data, if it looked promising the first time, it will by definition look promising again when it is re-presented. That being said, the data did look reasonable. Certainly, adding a PD-1 or PD-L1 inhibitor to chemotherapy appeared to increase the response rate. There also was an impressive progression-free survival. This was compared to chemotherapy alone, and it did look quite good.

Now, the concerns are: Is it better to use all of the agents together, or would it be better to sequence the agents? There are a host of issues that come up. The reason, of course, that this becomes a practical concern is that practitioners looking at the data from these studies may be inclined to take this data and extrapolate it to their practice even though it is not an approved approach. I would really caution people against that. One has to remember that often times in these early phase studies that the investigators look at a very highly selected patient population. This may not be appropriate for all patients and that there are several ongoing Phase III studies that are looking at this. And although we don't have much in the way of reports about what is being done outside of a clinical trial, I would really caution practitioners to wait on the results of the clinical trials testing these approaches and, if possible, refer patients, or if you have studies available, enroll patients at your own sites to explore these ideas.

Dr. Caudle:
If you're just tuning in, you are listening to Project Oncology on ReachMD. I am Dr. Jennifer Caudle, and I'm speaking with Dr. Edward Garon. We are talking about treatment updates for non-small cell lung cancer that were presented at the World Conference on Lung Cancer's Annual Conference.

So, moving forward, as a follow-up to our last question, are you seeing use of agents targeting checkpoint inhibition such as an anti PD-1 in small-cell lung cancer or mesothelioma outside the context of clinical trials? If so, under what circumstances?

Dr. Garon:
Again, this is not something where we are going to see a lot of data, but my experience is, particularly having a practice of my own which often also sees patients in second opinion who are getting treatment elsewhere, and I would say that we are seeing a substantial usage of checkpoint inhibitors directed against the PD-1 immune checkpoint in both small cell lung cancer and mesothelioma. I think that
between ability to either get these agents through insurance or through compassionate care, that these agents often are being used in that context even in the absence of approval.

Now, in some respects, this makes it difficult to enroll on clinical trials that would, in fact, show the benefit of these agents, and that, of course, in some ways is unfortunate because we know that sometimes what looks like promising data in these fairly rare diseases, when one looks at adding them in a randomized fashion doesn't necessarily pan out. And, in fact, with both of these agents, there was recent data that was presented in placebo-controlled studies looking at CTLA4 inhibitors, that the class of drugs had looked promising in early data, but in fact, in the Phase III study both of them failed to show any benefit over placebo. So, in an ideal world, I certainly think that it is important to evaluate PD-1 inhibitors in small cell lung cancer and mesothelioma in order to demonstrate whether there is, in fact, a benefit. That being said, certainly in talking amongst my colleagues and seeing patients in second opinion, these agents clearly are being used in that category of patients off label at this time.

Dr. Caudle:
Do you expect that within the next year all patients with non-small cell lung cancer will be receiving an inhibitor of the PD-1 immune checkpoint plus a CTLA4 inhibitor? Has anything emerged at the conference about this?

Dr. Garon:
There was another dataset from a fairly small dataset like the KEYNOTE-021 G dataset that I mentioned before. This one was really two specific cohorts from the CheckMate 012 study. That study looked at the combination of a CTLA4 inhibitor as well as a PD-1 inhibitor. In that instance it was nivolumab and ipilimumab. This data was a re-presentation of patients who had already been presented, although at this meeting there was longer follow-up data, so more mature progression-free survival data was presented.

The data looked extremely intriguing. The response rate was 43% for the combination of ipilimumab and nivolumab. They had a similar cohort, although it was not randomized, looking at nivolumab as part of the same study, and there the response rate was around 20%, and 20% really has been what has been seen across the board for this class of drug. So, on some level this data was very encouraging. The progression-free survival was quite impressive. In fact, it was more than double in this small subset of patients.

That being said, I had the opportunity to be the discussant when this data was presented, and I think there are some concerns we could have regarding patient selection. We know that patients in the earlier cohorts of this study where the ipilimumab was given every 3 weeks along with nivolumab on a more typical schedule that, in fact, the patients did run into significant problems with toxicity. And in the
cohorts that were presented, that was addressed by giving the ipilimumab every 6 or 12 weeks. Again, the results looked quite impressive in that group, but the numbers are fairly small, and I think the thing we still have to be concerned about is whether or not these effects are based on the improved outcomes from the combination versus the possibility that the investigators selected a more robust group of patients for this combination which is known to be more toxic, for instance, than single agent PD-1 inhibition.

Dr. Caudle:
Well, before we wrap up, is there anything you would like to revisit or a topic that we have not discussed that you’d like to discuss for our learners?

Dr. Garon:
I think that the only thing that I would add is that I think it is going to be very important as we move forward to evaluate agents in careful clinical trials. I think that there are almost an enumerable number of clinical trials that are going on that are testing PD-1 inhibitors with another agent, and with so many trials, even just by chance there will be some that will look quite good. And I think that as we are getting this huge amount of data in the next year or two, I think that it will be very important for practitioners to be cautious. I think that the benefits that we have seen with PD-1 and PD-L1 inhibitors has been tremendous and really not the sort of thing that we have seen all of the time in lung cancer or cancer in general. And while I am hopeful that we will just continue to march forward with every combination that we try, we know that that is unlikely, that the benefits going forward are likely to be based on careful science. And I think it will be very important as data emerges, some of which will look promising, for practitioners to demand really high-quality data before making changes in the way they treat patients.

Dr. Caudle:
Well, with that I very much want to thank my guest, Dr. Edward Garon, for talking with me about current and emerging immunotherapies and the treatment of non-small cell lung cancer presented at the World Conference on Lung Cancer.

Dr. Garon, great to have you with us. Thank you.

Dr. Garon:
Thank you.

Narrator:
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