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Highlights from ESMO 2016: The Continued Rise of Anti-PD-1 Therapy in the Treatment of NSCLC

Narrator:

Welcome to *Project Oncology* on ReachMD and the Prova Education activity, Highlights from ESMO 2016, the "Continued Rise of Anti-PD-1 Therapy in the Treatment of Non-small Cell Lung Cancer."

Your host is Dr. Matt Birnholz. Dr. Birnholz will speak with Dr. Edward Kim, who is Chair of Solid Tumor Oncology and Investigational Therapeutics, and the Donald S. Kim Distinguished Chair for Cancer Research at the Levine Cancer Institute, Carolina's Healthcare System in Charlotte, North Carolina.

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Dr. Birnholz:

Lung cancer is the leading cause of cancer-associated mortality with almost 225,000 new cases and over 158,000 deaths estimated in 2016 in the United States alone. Non-small cell lung cancer represents approximately 85% of those cases which makes the need to better identify and treat this disease absolutely critical. This is Project Oncology. I'm Dr. Matt Birnholz. My guest, Dr. Edward Kim, will review the data on non-small cell lung cancer presented at the Annual ESMO Conference in Copenhagen, Denmark. We'll discuss the expanding therapeutic rolls for anti-PD-1 checkpoint inhibitors and other emerging therapies, as well as the value of biomarkers for identifying patients likely to respond better to immunotherapy. Dr. Kim, welcome to the program.

Dr. Kim:

Thank you.

Dr. Birnholz:

Great to have you with us. So, to start off our discussion, what is the current state of approved immunotherapy agents for non-small cell lung cancer?

Dr. Kim:

We have been blessed recently in the treatment of non-small cell lung cancer as there have been numerous agents approved for treatment and this always benefits patients. Just in the past year and a half, we've had six or more agents approved and they've all been targeted therapies which, again, is changing the paradigm of our approach toward treatment of patients. An exciting area which

has emerged from melanoma and renal cell has been these checkpoint inhibitors. We currently have two of them that are approved for utilization in patients with non-small cell lung cancer. One of them is called nivolumab. This drug was FDA approved as a second-line agent after treatment with a platinum-containing agent and is available for patients who are fit enough and don't have any contraindication to be treated as a second-line agent who have both non-squamous and squamous cell lung cancers. The other drug is pembrolizumab. Now that drug also has been FDA approved in the second-line setting post a platinum-containing regimen, but with one caveat that you do have to have a positive expression of PD-L1, which is a marker that we would measure on the tumor cell. This is the difference between the two indications but, essentially, they have very similar efficacy and safety profiles.

Dr. Birnholz:

That's great. And you mentioned PD-L1 and I want to turn to the current biomarkers of interest. Is PD-L1 the central biomarker or are there are other biomarkers of interest when considering immunotherapy?

Dr. Kim:

It's interesting how this arena has evolved. It's very similar, maybe to how EGFR evolved over a decade where there were many different markers and finally it consolidated into a single biomarker or, I would say, a single group of biomarkers that we use for testing. PD-L1 started the same way. I think where we were confused was early on with the approval of these drugs in other tumor types, there was no testing needed, and there wasn't seen a lot of correlation between the marker expression, or any other markers, and efficacy. And then, with the approvals in lung cancer, we now have a marker present, in one indication and not in another. And so, there has been some questions about whether a high expression versus a low expression on a PD-L1 marker is of value. There are subsets that have shown that perhaps it is. People started looking at other markers as well, and this included mutational burden, which has been described for several years and is now being one of the markers testing to see if patients actually can get better efficacy. And there are some companies now that are adding mutational burden, mutational load, onto their marker panel so that one can make a determination of whether a checkpoint inhibitor is appropriate or not. It's important to note, though, that there is no FDA indication with any of these other markers, other than PD-L1 expression, with any of these drugs. But we are seeing trends that, in fact, expression may correlate with some benefit in certain drugs.

Dr. Birnholz:

So then, if we stay with PD-L1 as the FDA-approved marker, what are the current testing requirements for using PD-L1 for non-small cell lung cancer?

Dr. Kim:

This is what really made the market a very dichotomous area. As I said, both drugs are very similar in their efficacy profile, that being pembrolizumab and nivolumab. They're very similar in their indications, second line, post platinum-containing regimen, as far as prior treatment, as well as side effects. There are little differences in dosing. One is every 3 weeks, the pembrolizumab, and nivolumab is every 2 weeks. But the difference on the label was that in order to dose pembrolizumab you need an expression of PD-L1. There is sometimes a disconnect as well between what a positive PD-L1 expression level is and what is reimbursed. And so, what evolved during the first year of the indication was that really any CLIA-certified test that showed that there was present a staining, 1+ or more, of PD-L1 on these tumor cells led to the availability of utilization of pembrolizumab. That's not as scientific as we would like to be, because we would assume that there's a certain expression level, whether that's 5%, 10%, or 50%, that the drug may be more active in. But based on how the approval was with the drug and how the dosing and the drug doses were, this was as best as we could get them. And certainly that, I think, led to many people's practices of administering one of these drugs, to be that of nivolumab, because there was no requirement for any PD-L1 testing, and so it was easier to just proceed with treatment with the drug.

Dr. Birnholz:

So given then, what you just talked about with practice trends from these testing requirements, what would you say the future state of anti-PD-1 is as a frontline therapy for non-small cell lung cancer?

Dr. Kim:

Well, this is where the groundbreaking work has been presented, most recently at the ESMO Meeting, and there had been a buzz ever since the summer regarding the frontline approaches. Now, a year ago, roughly, we had the indication that second-line treatment was where the approvals were, but we know that as companies, as research, as investigators, and certainly as patients, we want to see if there can be expanded utilization. And those questions naturally come up with drugs that have activity. So there are many efforts in the frontline setting to test and see what the value of these drugs are. Now, one of the early tests was using the single-agent, so that was either nivolumab or pembrolizumab, and going head-to-head versus a doublet chemotherapy. Doublet platinum-based chemotherapy has been the foundation of lung cancer treatment for as long as I can remember. When I finished my fellowship back in 2001, that was the standard, and ECOG 1594 was presented on the ASCO Plenary Session and published in the *New England Journal of Medicine*, showing that either any doublet chemotherapy led to the same survival. So, this has been the bar to achieve over the years to see if there was something better. We heard the results at ESMO of two trials that reported results, very similar design, of a single-agent PD-1 inhibitor versus doublet chemotherapy. The data with pembrolizumab proved to be superior versus doublet chemotherapy and that was with the caveat that it was in a PD-L1 marker-positive population and the positivity, the expression, had to be greater than 50%. So this is a definitely an enriched population for whose tumors have PD-L1 positivity, about 25% of the lung cancer, non-small cell lung cancer population, and the hazard ratio for survival, overall survival, was 0.6. That's astounding. And this was a trial that was stopped early because it was proving superior to doublet chemotherapy which had similar efficacy as past trials and historical standards. So, this is truly a practice-changing study that will change how we assess patients. We will now order several biomarkers and including to EGFR mutations and ALK translocations, and ROS-1, we'll also include PD-L1 expression. And for those patients whose tumors harbor greater than 50% expression, they can be offered single-agent pembrolizumab as opposed to doublet chemotherapy. That's just huge regarding now pathways, guidelines, and practice, the standard of care.

The corresponding nivolumab study, the results had come out about a month prior to the meeting, and demonstrated that there was not an improvement of single-agent nivolumab versus doublet chemotherapy. And so, we now have this other separation a year later that has occurred between the two drugs. The first was in second-line where there was some inconvenience with testing, because the data was very similar between the two agents, and now we're going to mandate reflex testing, at least at our center, of anyone who comes in, to see if the PD-L1 expression in their tumors is high and offer them pembrolizumab. So, truly outstanding regarding the treatment paradigm, which has changed. We'll also look forward to seeing what the combination data is. There was some combination data with chemotherapy in addition to a checkpoint inhibitor presented in the first-line setting. That data was in a small subset of patients of a larger trial, and did show some very interesting efficacy results, but we'll see more of those results next year at the major meetings.

Dr. Birnholz:

If you're just tuning in, you're listening to Project Oncology on ReachMD. I'm Dr. Matt Birnholz and I'm speaking with Dr. Edward Kim. We're talking about biomarker and treatment updates for non-small cell lung cancer that was presented at the ESMO Annual Conference. So, Dr. Kim, carrying forward what you just talked about, all this compelling data clearly indicates an emerging paradigm shift in treatment, a huge impact, for this emergence of anti-PD-1 therapies. Given that, given the expected shifts in treatment, do you see an expected timeline anticipated for when this kind of impact will fully take shape in practice?

Dr. Kim:

Yes, much of our timelines of how we practice are determined by first the studies and their results, second is the regulators and when the labels can be adjusted, and third is the payers. We have to be fortunate in the United States that we now have a quicker process to get these drugs into the hands of patients so that they can receive treatment. I think the paradigm is changing right in front of us, and as this year we will shift toward testing with PD-L1 positive tumor types, and seeing if those with high expression, those patients who'll be eligible for getting a single agent drug instead of doublet chemotherapy. We are continuing to shrink the percentage of patients who walk through the door that will get one-size-fits-all treatment. We are continually now moving toward a personalized precision medicine paradigm where we will be able to test patients, whether it's their tissue, their blood, their urine; we'll be able to measure markers, not just for scientific and research interests, but that have clinical applicability where we get the results, it will help us determine which therapy is best for that patient. And this is a great thing. This is what we've wanted. This has been the breast cancer paradigm with hormone and HER-2 for quite some time and now in lung cancer, finally, one of the largest cancer types across the world, we're going to

start seeing changes. So, they key now is to make these tests and make these drugs available so that the providers can offer them to the patients.

Dr. Birnholz:

It seems, therefore, that one of the most monumental applications down the pike for anti-PD-1 is this trend towards more personalized therapeutic approach. What about other future applications? Do you envision a move towards adding anti-PD-L1 in combinations with, for instance, doublet chemotherapies, or perhaps as adjuncts to radiotherapy?

Dr. Kim:

It is one of those paradigms where if we get a drug or a drug class which has a good safety profile, a good efficacy profile, and has multiple indications, we're going to want to start to play with it more. And usually the paradigm is, we start with the multiply-treated patient in the advanced setting and move it up. So the next step is, after second-line, first-line. After first-line metastatic, now we start looking at the locally advanced setting and that would be either in combination with chemotherapy, as a maintenance given after concurrent chemo or radiation, or other settings like that. And then, to the early stage, post surgical setting. What we also mimic, if we look at the melanoma and renal cell world is that they too started with single agents with treatment and then used combinations. The combinations of using a CTLA-4 plus PD-1, or incorporating some of the interesting PD-L1s with these combinations, is certainly being tested actively. There are also dozens of TKIs that are being tested in combination with the PD and PD-L1s, so to try and find that sort of biological rationale of combining these drugs to further push the efficacy. We, at the Levine Cancer Institute, are testing many of these combinations with some very interesting results, and I think we're just going to see more and more of that. As the data comes out next year, especially in the upfront setting, looking at combination CTLA-4s and PD-1s or PD-1s and TKIs, it's going to shape which direction we go next. But we've already seen some activity in small cell, for instance, with a combination of ipilimumab and nivolumab, so we're anticipating those results next year and hopefully they'll show a difference, and we might further change the paradigm of, rather than giving doublet chemotherapy, it might be a single PD-1 or checkpoint inhibitor, and then, perhaps, a double immunotherapy treatment with a checkpoint inhibitor as well as with a CTLA-4.

Dr. Birnholz:

And before we wrap up today, Dr. Kim, there's also been a lot of attention swung recently towards the emerging IDO inhibitors. Can you talk about what role these therapies could play right now and when you think they might reach the clinic?

Dr. Kim:

Well, immunotherapy is the hot area and it's a hot area now for anyone in drug development to look at other mechanisms. I think, after years of testing vaccines and not seeing the results that we would like to see, now looking at specific mechanisms within sort of the immunobiology part of the cell, is what's fascinating. And so, IDO or indolamine 2,3-dioxygenase, it's one of another immune checkpoint and it's involved in, again, the tumors escaping the immune system. So, this IDO enzyme which is activated in dendritic cells and macrophages, it creates this environment almost, this wall, that favors suppression and tolerance. And so, if you're able to suppress the immune system, that's where you can overcome it. And this is the mechanism that's thought, too, with IDO. So, if you see IDO expressed and there are multiple tumor types including melanoma and GYN tumors and others that it is expressed in, higher IDO expression appears to correlates with poorer outcomes, again in multiple cancers. And so now, if we can get these IDO inhibitors and block that mechanism, which is a different mechanism than the traditional checkpoint inhibitors, then maybe combination strategies in that manner, similar to how we're doing it with CTLA-4 and PD-1, could also be a novel mechanism or novel combination mechanism to further help overcome this resistance that the tumors have. And this would include with any of the PD-1s or PD-L1s. We have pembrolizumab and nivolumab. We've recently got atezolizumab which has been FDA approved for bladder cancer, that's a PD-L1, and then, durvalumab is close behind. So it's nice to have this menu of options with multiple different agents and then adding to the combinations of these new IDO inhibitors, in addition to the CTLA-4s, with the TKIs, and chemotherapies that we're looking at for combination, it's just so many moving parts over the next year or two. It's going to be fascinating to see how these results come out. And no one would be happier than the patients or the providers, if we could continue to narrow down the number of patients that just get one-size-fits-all chemotherapy, and really start working on a more precision-medicine approach.

Dr. Birnholz:

Well, with that great parting thought, I very much want to thank my guest, Dr. Edward Kim, for talking with me about Current and Emerging Immunotherapies in the Treatment of Non-small Cell Lung Cancer, presented at the ESMO Annual Conference. Dr. Kim, it was great to have you with us.

Dr. Kim:

Thank you. It's my pleasure.

Narrator:

This segment of Project Oncology on ReachMD is brought to you by Prova Education. Since the recording of this interview, atezolizumab was approved by the FDA on Oct. 18, 2016 for use in Non-small Cell Lung Cancer. To receive your free CME credit, or to download this segment, go to ReachMD.com/ProjectOncology on your smartphone or tablet device. Thanks for listening.