Immunotherapy for Squamous Non-Small Cell Lung Cancer

TRANSCRIPT
**Dr. West:** Hi, I’m Dr. Jack West, medical oncologist from Swedish Cancer Institute in Seattle, Washington, and the founder and president of GRACE, Global Resource for Advance in Cancer Education.

I’m here at the tail end of the ASCO conference, the American Society for Clinical Oncology annual conference, which is the largest cancer meeting of the year, and I’m happy to be joined this morning by two of my colleagues, Dr. Jean-Charles Soria from Villejuif, France – he is a professor and the Chairman of Drug Development; and Dr. Leena Gandhi from Dana Farber Cancer Institute – she is an Assistant Professor there; both are lung cancer specialists and experts who presented at this meeting and also reviewed the content. Today we’re going to be talking about some of the highlights and the potential clinical implications of it.

So, good morning and thanks for joining us.

**Dr. Gandhi:** Good morning.

**Dr. West:** Alright, this year’s meeting was really dominated, I would say, by immunotherapy, as at least where a lot of the enthusiasm was. There was a lot of great work in many areas, but some of the bigger stories were with immunotherapy, and one of the leading ones was the CheckMate studies which were with nivolumab (or Opdivo), an anti-PD-1 immune checkpoint inhibitor that was compared with Taxotere (or docetaxel) in the second-line setting.
Leena, can you talk a bit about the heavily anticipated CheckMate 017 trial in the squamous population and what you thought of the results?

**Dr. Ganghi:** Yeah, I mean these were parallel studies, one done in squamous cell patients and the squamous cell results were actually – a little hint of it was already given because it led to approval even before this meeting – of the drug. There was an improved survival with Opdivo compared to docetaxel and basically a significant increase in the one-year survival, overall survival, and an increase in the median progression-free survival as well. I think that we all expected there to be some survival benefit knowing what we know about PD-1 inhibitors – that they, when they do lead to responses, they lead to very durable responses; and there is a tail of the curve, meaning that there are patients that survive for very long periods of time, and that’s what we hoped to see. I think what was a little more unanticipated is the difference between the two curves all along the way, including at early stages and at median progression-free survival. I think that speaks more to the fact that docetaxel is a poor standard that we have in squamous cell carcinoma. It doesn’t take much really to beat that, as we know from prior studies that lead to approval of ramucirumab or nintedanib, which I don’t really think showed really much difference at all. Here, I think there really is a much more clear cut difference, there is obviously improved toxicity, and I think it has already shifted the standard of care, even prior to this meeting.

**Dr. West:** Right, and this probably only cemented that, that I would say that especially with nivolumab (Opdivo) commercially available in the U.S., that people are moving, and if they haven’t, are on their way to completely switching to that as the second-line standard.
Another interesting aspect that was they looked at PD-L1 expression in this, which is a marker that has been equivocal for its ability to predict patients who will or won’t benefit from these immunotherapies, and in this trial there was no association with response in the squamous population.

**Dr. Gandhi:** Yeah, I mean I think you have to take those results with a grain of salt. One is that there are different potential predictors of benefit: one is PD-L1 expression, one is potentially smoking status which may be higher overall in the squamous population, and one is mutational burden which may be higher overall in the squamous population, and we don’t know to what degree those factors overlap or how independent they are in terms of predictive value. When you actually looked at the curves for greater than 1%, 5%, or 10%, there is a slight increase, and I suspect that if you looked further at that you would see a difference. We know that PD-L1 expression is a continuum; the higher the level of PD-L1 expression, the higher the potential benefit, and that’s been shown across multiple drugs. We don’t know how to exactly compare this to pembrolizumab, where they have not seen a difference in overall outcome for PD-L1 expression below 50%, but above 50% there’s a clear different and a real separation of the curves. I wonder if you looked at higher levels of PD-L1 expression here, whether you might see the same thing.

**Dr. West:** Jean-Charles, what did you think of the results, and what is going to be the clinical practice in France or much of Europe based on both the legal situation and what’s permissible, and general sentiment?
Dr. Soria: Thank you, Jack, for inviting me, and the opportunity to discuss this very interesting work. I agree here, this is a very important study, and it is clear that we need to rejoice by the fact that over the last two years, squamous cell carcinoma, which was really a poor disease with patients with many comorbidities, because it’s highly related to high exposure to tobacco, they had basically only two options in the second-line setting: namely docetaxel or Tarceva. And now we have, in just this one year, have ramucirumab coming in and now nivolumab coming in. I agree, nivolumab’s level of benefit is really outstanding, and this is something important. The situation right now is that compassionate access is possible for squamous cell carcinoma of the lung, in France, and I am sure we are going to have a discussion on the price; that is not going to be the price you are applying in the United States, because what the European market can bear, or the economy, will not be the same. So, I wonder what’s going to be the price. It’s been currently discussed as being €7,400/month in France, which is basically much cheaper that what you are getting here in the U.S., where the price per month is above $13,000. But this is great news for the patients, wherever they are. I hope this drug is going to be available rapidly.

In terms of markers and predictive biomarkers, I fully agree with you, Leena. This is not yet something that – the jury is out. I think we have clearly people who want to, say, all comers, all benefits, and I don’t think that’s black or white. I really think there is something about PD-L1 expression, in its own fine-tuning, but remember, it took us 15 years to agree on how we define an estrogen receptor-positive breast cancer, so it might take us a few years to define a PD-L1-positive lung, and I agree that the idea of classifying tumors
by mutation alone might be the way to go, correct? We are doing molecular screening for our patients.

So I predict to see tomorrow, a report that will tell you not only whether this patient is Ras-mutant or EGFR-mutant, which is rare in squamous, but on top of that, you can have mutational index – high, intermediate, low – and that might also guide your therapy.

**Dr. West:** Well, it’s a good point that the field has been moving so quickly that we’re living through it – it’s evolving almost month-to-month, and certainly meeting-to-meeting as we get new results.
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