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Highlights from Singapore on Immunotherapies in Early-Stage NSCLC

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Dr. Forde:
Welcome, everybody. My name is Dr. Patrick Forde. I'm a Medical Oncologist in the Thoracic Oncology Group at Johns Hopkins. And I'm delighted today to join with Dr. Charu Aggarwal, a Medical Oncologist at the University of Pennsylvania, to discuss some of the recent data from the World Conference on Lung Cancer in Singapore. Some exciting data became available.

First of all, I'd ask Dr. Aggarwal to introduce yourself and perhaps give some brief thoughts on the conference as a whole.

Dr. Aggarwal:
Thank you, Dr. Forde. I'm Charu Aggarwal, I'm the Leslye Heisler Associate Professor for Lung Cancer Excellence at the University of Pennsylvania. It's a pleasure to be here to discuss some recent updates. I think it was a really good conference, a lot of data being presented both in targeted therapies as well as immunotherapy with a special focus on early-stage lung cancer, and I look forward to reviewing this with you.

Dr. Forde:
Excellent. Well, just to dive right in. What we saw in this conference really were some new data we've had multiple approvals in early-stage lung cancer for immunotherapy. First of all, in the adjuvant setting with the approval of atezolizumab now several years ago, and also more recently, the approval of adjuvant pembrolizumab. But the last year and a half or so has really been focused on the neoadjuvant setting. And we're starting to see some novel studies in this setting. And one of those trials was a Swiss trial called SAKK 16/18. This was a study looking at the incorporation of chemotherapy plus immunotherapy, in this case durvalumab, along with immunomodulatory radiation, so lower dose radiation than normal to the primary tumor. This builds on work done by Dr. Altorki and colleagues in New York, which looked at sub-ablative radiation combined with durvalumab, and suggested encouraging results. In this trial, SAKK 16/18, the main endpoints were really looking at the number of patients who got to surgery, was the treatment safe, and also what the pathologic response rates were. So in this study, over 80% of patients were able to receive definitive surgery. This lines up well with the data we've seen from phase 3 trials of chemo IO. So it doesn't suggest that radiation at least reduces the risk of getting the surgery. And the results in terms of pathologic response, perhaps similar pathological complete response rates to what we've seen with chemo IO. However, somewhat higher major pathological response rates in the 70 to 80% range. And I think that's an interesting finding, perhaps we're seeing some increase in those patients who don't achieve a PCR, but have a good pathologic response.

Charu, have you further thoughts on the study?

Dr. Aggarwal:
So I think, as you said, Patrick, very feasible. There were different arms being evaluated with different radiation schema. You know, it seemed like it was very feasible to integrate it, but again, I think very small numbers, and we need to see this in a larger population.

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Often with these small studies, the patients are quite selected. So you know, I think how do we apply this to other patients as well as larger centers or even smaller centers that may not have the expertise to deliver these radiation therapy techniques?

Dr. Forde:
Yes, I agree completely. It'll be interesting to see how this concept of lower dose radiation in early-stage lung cancer, perhaps being immunomodulatory, pans out. And I think we're going to see more and more studies in this setting.

Moving on to a study called INCREASE. And this study looked at performing surgery for early-stage lung cancer after standard-dose chemo with immunotherapy and radiation. And I think here, we did see perhaps some signal again. A single-arm study, so not definitive in any way, but very high pathological complete response rates of about 60%. But the flip side of that is we also saw very high rates of toxicity, grade 3/4 toxicity rate was 73%. And that's roughly double what we expect with chemoimmunotherapy alone in this setting.

Charu, any thoughts on this trial, the potential incorporation of radiation with standard chemo IO in the neoadjuvant setting?

Dr. Aggarwal:
I think the PET-CR rates look incredible here. And I think if we can continue to move up the needle on PET-CR rates, that's what we all want, because it ultimately translates potentially to cure. But again, I think early signal, safety is important, and we need to look at larger data.

Dr. Forde:
Exactly. And I think one of the bigger questions in the long-term is whether a pathologic complete response from radiation is going to mean the same thing as one from systemic therapy alone, and I think that's something we will only find out with more and more of these trials.

Moving on to one of the adjuvant trials, the major studies recently where we had an update on looking at some of the translational science, in this case IMpower010. This was the trial which led to the approval of adjuvant atezolizumab after adjuvant chemotherapy for PD-L1 1% or above resected non-small cell lung cancer. And this study presented the World Conference in Lung Cancer looked at whether tumor mutational burden, which we've looked at a lot in advanced lung cancer, could influence both the prognosis but also the benefit from adjuvant atezolizumab. The results from this analysis essentially suggested that those patients who had higher rates of TMB, higher numbers of mutations in their tumor, had prolonged disease-free survival. But there was benefit seen from atezolizumab in both high and low TMB. And some of the context here is that in some of the other trials in particular, CheckMate 816, which was a neoadjuvant trial, the TMB didn't appear to influence neoadjuvant immunotherapy to a dramatic degree. Perhaps we're seeing here a prognostic impact, but again, benefit for both high and low TMB.

What were your thoughts on this, Charu?

Dr. Aggarwal:
Not surprising at first glance, you know, we would expect that patients with higher TMB, or TMB-high would have improved median DFS. This is sort of very similar to what we would expect from the metastatic setting. And I think we will begin to select patients based on PD-L1 level but also potentially smoking history as a rough surrogate of TMB in clinic. Most of our NGS reports have TMB on them. So I do think that this will become sort of like a surrogate marker of increased response. And I agree with your observation that these may not be that important in the neoadjuvant setting when we're administering them, especially with chemotherapy, as we've seen responses even in PD-L1 negative patients, but I think as we think about delivering immunotherapy in the absence of tumor in situ, I think it's important to think about overall TMB as well as PD-L1 and smoking history.

Dr. Forde:
Perfect. Yep. Great summary.

Moving – well, actually sticking with the perioperative setting for stage II and III non-small cell lung cancer, and we did have an update on the surgical outcomes from the AEGEAN trial. This was a study presented at the AACR meeting earlier this year by Dr. Heymach, looking at neoadjuvant chemo plus durvalumab, followed by adjuvant durvalumab versus chemo alone in the neoadjuvant setting. That showed a significant benefit from durvalumab addition in terms of event-free survival. And the update at World Conference in Lung Cancer looked at the surgical outcomes. And in general, at least in my view on the AEGEAN surgical outcomes, they appear similar to CheckMate 816 in some ways, in that there didn't appear to be any real decrement from adding durvalumab in the neoadjuvant setting. Patients did at least as well with chemo/durvalumab versus chemo.

There was a second presentation looking at the role of durvalumab in the neoadjuvant setting for patients with EGFR-mutated lung cancer. This is one of the - or it is the first real subgroup analysis looking at this population, and it doesn't appear as if there is a significant benefit for those patients with EGFR-mutated lung cancer from neoadjuvant chemo with anti PD-L1 in this case.

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So two findings which we might have expected, really from prior data, but I think the more data we can glean in this setting, the more helpful it will be. Any further thoughts on those two presentations, Charu?

Dr. Aggarwal:
No, I think it further refines our thinking of this trial and how we will incorporate this into our clinical practice. I think molecular testing is going to continue to be key in early-stage setting to personalized therapy.

Dr. Forde:
I agree, and I think it's important especially in the neoadjuvant setting to keep in mind that really, so we don't have a strong indication at present for neoadjuvant chemo immunotherapy for patients with EGFR-mutated lung cancer, whereas we do have a strong indication in the adjuvant setting for adjuvant osimertinib.

And finally, moving on to stage I disease. Now, all of these developments really with chemo IO and IO in the perioperative setting have focused on either larger tumors or node-positive disease. So stage II and IIIA. But there was a study presented at the World Conference on Lung Cancer looking at the incorporation of SBRT, or stereotactic body radiation for stage I, or very early-stage lung cancer, is incorporated with immunotherapy. And this showed encouraging results. It was a randomized study looking at this incorporation of immunotherapy showing that at 2 years, event-free survival was about 77% in those patients who had immunotherapy, versus 53% and those who did not. And I think we should keep in mind that even early-stage lung cancers still have a relatively high rate of relapse of about 20% or so or more. And I think this is a kind of a key finding here as well.

Any further thoughts on that, Dr. Aggarwal?

Dr. Aggarwal:
I think a phase 3 randomized study is potentially needed to establish this as a standard of care. These studies take a long time to approve, but I think are so essential in our understanding and delivery of care for these patients.

Dr. Forde:
Exactly. Well, thank you very much.

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