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Highlights from Madrid on Perioperative Immunotherapy in Early-Stage NSCLC

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Dr. Forde:
Hello, my name is Dr. Patrick Forde. I'm a Medical Oncologist at Johns Hopkins University in Baltimore, Maryland. And I'm joined today by Dr. Charu Aggarwal, the Leslye Heisler Associate Professor of Medicine at the University of Pennsylvania. And we're going to discuss some of the recent findings in the realm of perioperative therapy and immunotherapy for non-small cell lung cancer.

Charu, it was quite a remarkable meeting in many ways, both in terms of targeted therapy and also early-stage lung cancer.

Dr. Aggarwal:
Absolutely, I think this was one of the meetings with the most lung data has come out in one meeting, three packed days.

Dr. Forde:
Exactly. And I think it was we – I think we as a field and lung cancer took up a lot of the presidential sessions, which is very encouraging.

First of all, I'm going to talk a little bit about the CheckMate 77T trial which was presented by Dr. Tina Cascone from MD Anderson. Now this is the fourth either neoadjuvant or perioperative phase 3 trial to report out. It's the third perioperative trial after the AEGEAN trial and the KEYNOTE-671. In this trial, 459 patients were enrolled, who received either a control arm of four cycles of neoadjuvant chemotherapy. The chemotherapy could be either carboplatin or cisplatin based, or an investigation arm received the same platinum doublet chemotherapy plus nivolumab. In the investigational arm, patients received 1 year of adjuvant nivolumab. So a key difference between CheckMate 77T and CheckMate 816 is that there was one more psychotherapy in the neoadjuvant setting, and 1 full year of adjuvant immunotherapy, whereas CheckMate 816 was just neoadjuvant therapy.

Overall, the arms and the trial were well balanced. So as we see in many of the neoadjuvant and perioperative trials, the stages skewed towards stage III, 64% of patients in the trial have clinical stage III disease, and about 56% of patients have PD-L1 1% or above positive disease. In terms of the dispensation of the patients in the trial, 78% of patients in the neoadjuvant chemo plus nivolumab arm had a definitive surgery for their cancer. And we're seeing that across the perioperative trials, anything from 78 to 85% of patients in the chemo IO arms are actually having definitive surgery. Once patients had surgery, 62% of the intention-to-treat population commenced adjuvant treatment, and approximately 2/3rd of those patients who commenced adjuvant, completed it.

So I think one thing to bear in mind in terms of perioperative trials is that while nearly all patients start the neoadjuvant therapy, nearly all patients complete the neoadjuvant therapy, not all patients get through the full course of treatment of more than 1 year. 77T was a positive study for the primary endpoint of event-free survival with a hazard ratio of 0.58 favoring chemo plus nivolumab. Interestingly enough, this is exactly the same hazard ratio for event-free survival as in KEYNOTE 671. Most of the benefits for event-free survival here was seen in stage III disease which is what we've also seen in the other clinical trials with a hazard ratio of 0.51 favoring chemo/nivolumab for that group. Also those patients who had PD-L1 positive disease were more likely to have a good outcome. Indeed, more than 50% of patients who had PD-L1 high lung cancer in this trial had a pathological complete response. And in the overall population, the PCR ratio was 25.3%.

So overall, CheckMate, 77T was a positive trial and shows that the perioperative approach delivers significant benefits for patients. And I think one of the key questions here is as this trial matures and as CheckMate 816 also matures, which patients benefit just from neoadjuvant therapy? And which patients will benefit more from a longer course of perioperative?

Charu, what are your thoughts on this trial?

Dr. Aggarwal:
I think this trial adds to our emerging excitement around perioperative therapy. This is the third trial to really hone into this idea of both neoadjuvant and adjuvant clinical trials. We have seen positive data from a AEGEAN, KEYNOTE 671, and now CheckMate 77T. I do think that this only establishes that we should potentially be using perioperative therapy for almost all our patients, given the signals that we are seeing, not just with PET CR or EFS but also in terms of early data for overall survival. And I think this is something that is going to change management and change pathways at several institutions.

Dr. Forde:
Yeah, and I think that's a good pathway into discussing and KEYNOTE 671. We had updates from several other phase 3 trials at ESMO, one of which was the perioperative study of chemotherapy plus pembrolizumab. And this was updated by John Spicer, looking at overall survival, which has matured. And this shows that those patients who received perioperative cisplatin-based chemotherapy with pembrolizumab, now have a significantly improved overall survival compared to chemotherapy alone with a hazard ratio of 0.72, favoring the chemo/pembrolizumab arm.

Some of the subsets were also presented by Dr. Spicer. There's very significant benefit, as I mentioned, for higher stage cancer, also for PD-L1 positive disease. So many other subgroups I think will continue to follow for long-term outcomes. And indeed, here in the United States, the KEYNOTE 671 regimen was approved by the FDA just prior to the ESMO meeting. So a very exciting week in terms of new options for early-stage lung cancer.

Charu, what are your thoughts in terms of our first immunotherapy trial, either neoadjuvant, adjuvant, or perioperative, to show an overall survival benefit?

Dr. Aggarwal:
Absolutely. I think it's so exciting. We have been waiting to see overall survival updates from many of these perioperative trials, either neoadjuvant alone or, you know, I think, also the adjuvant trials. We think that the signal that we're seeing with KEYNOTE 671 will formally change our treatment paradigm to adopt a perioperative approach. And I think ultimately overall survival is the ultimate arbitrator.

Dr. Forde:
I agree. And I think we had two updates as well from CheckMate 816. Dr. Mariano Provencio presented 3-year results on the chemotherapy plus nivolumab versus chemo alone comparison by PD-L1 status. And I think one key thing I would pull out of Dr. Provencio's presentation is at 3 years, those patients who have a pathologic complete response to chemo plus nivolumab, which I'll remind you is about 24% of patients, they do extremely well with a median – or with more than 95% of patients being alive at 3 years, among those patients who have a pathologic complete response.

And my thought is that perhaps this use of pathologic complete response might help inform our treatment decisions for patients in the postoperative setting. What are your thoughts on that, Charu?

Dr. Aggarwal:
Yeah, I would completely agree with that. And I think we ultimately will need more biomarkers to really select patients adequately for combination therapies potentially, or how to choose just beyond PD-L1.

Dr. Forde:
I agree. And Dr. Mark Awad also presented data from another arm of CheckMate 816, which was an exploratory arm looking at nivolumab plus ipilimumab. This exploratory analysis did show significant benefits for those patients who got an nivolumab plus ipilimumab with increased pathologic complete responses up to 20%, and also improved event-free survival. One interesting finding here though, in comparing doublet immunotherapy versus chemoimmunotherapy, was that those event-free survival curves do cross with nivolumab plus ipilimumab at the very early points. So there are some patients who do not respond to nivo/ipi, and perhaps in the short term do worse, but in the longer term have sustained benefit. And I think what this suggests to me is that we're not going to be rid of chemotherapy anytime soon for patients with early-stage disease.

What are your thoughts on Dr. Awad's presentation, Charu?

Dr. Aggarwal:
Exactly that, that I think chemotherapy is still a very critical role – is going to play a critical role in the management of these patients. And we're not quite there yet where we can select the right patients to omit chemotherapy. I think we need trials like this to inform us of what may be important and what is not important. So I think it's an important step in the right direction.

Dr. Forde:
I agree. And I think we also had during the ESMO meeting the publication of the AEGEAN trial led by Dr. John Heymach in the *New England Journal of Medicine*. However, during the conference, Dr. Martin Reck presented translational science from the AEGEAN study, and this looked at circulating tumor DNA at the evolution during neoadjuvant chemoimmunotherapy with durvalumab. In this analysis, just under half of the patients, 186 from 401 patients enrolled, were evaluable for a tumor informed circulating tumor DNA assay. In the arm of the study containing durvalumab, there was an earlier and more significant reduction in circulating tumor DNA. Indeed, so in the durvalumab-containing arm, 66% of patients had cleared ctDNA by the time of surgery, compared to 41% in the chemotherapy-alone arm. And indeed, those patients who cleared ctDNA, were significantly more likely to have a pathologic complete response. And one could envisage in the longer term that this could be one more biomarker which could help us decide, both in terms of perhaps in the distant future, which patients need surgery, but probably in the nearer future, how we can determine postoperative therapy for such patients.

What were your thoughts on the AEGEAN ctDNA analysis, Charu?

Dr. Aggarwal:
Yeah, I think this is, again, good data, ctDNA is going to be informative. But I just don't think we are there yet, Patrick. What this trial showed us was that ctDNA in the perioperative period can sort of correlate to what response you're going to ultimately achieve. But I think the bigger question is, can we use ctDNA in the postsurgical setting to really determine who needs adjuvant therapy or not? Do all patients with PET CR need therapy? Maybe not. Currently, clinical trials demonstrate that maybe even amongst those patients with PET CR, there is a slight advantage to receiving immunotherapy. But who are those patients who need that additional immunotherapy? I think needs to be answered by perhaps these biomarkers that can help us further select, so use PET CR as a biomarker then further refine using ctDNA, our approach in the postoperative management.

Dr. Forde:
I agree and I think so it's an exciting area, and I think perhaps our next developments will be more in terms of these biomarkers rather than novel drugs but I think it's going to be very exciting over the next few years. We will leave it there. We've just had a very exciting conference and both in terms of targeted therapy and immunotherapy for non-small cell lung cancer.

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