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Early Stage NSCLC: Do We Have the Right Drug, Dose, Timing, and Patient?

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Dr. Spicer:
Hi everyone. So, in this session we will be discussing the complicated and probably moving target question of whether we have the right drug, dose, timing, and patient for the perioperative application of immunotherapy. So maybe to start with the question of the drug. We have a growing number of trials. There are at least two or three trials that are resulting with different drugs and many more to come. Dr. Peters, does it matter, Anti-PD-L1, Anti-PD-1?

Dr. Peters:
Yes, this is a provocative question. You know, in advanced disease we had this question many times. The trials do not treat exactly the same, is it because these drugs really behave differently? I do not think we can really tell it today, affirm it today and be, I would say, certain or confident enough to tell these drugs really differ. They might differ. They target different epitopes. Some are Anti-PD-1, some are Anti-PD-L1. And remember, you have some ADAs, and you have anti-drug antibodies, which might be different from one drug to the other one. That is possible. But still today, I am not sure that it is clinically relevant to consider that the drugs are different. What was different in the trials was the strategy and the patients enrolled. So, I think I would prefer with all of these trials to try to understand the best strategy according to each patient characteristic than trying to really make a religion out of one drug better than the other one. I do not think that scientifically this would be as relevant as trying to understand how long who should receive immunotherapy.

Dr. Spicer:
I think those are really wise words and will certainly advance the field much faster at this point. Dr. Forde, we have some data indicating that you know, chemo combined with IO will result with higher pCR. Some suggestions that maybe three doses are superior to two doses for achieving pCR, but no real translation in terms of survival on that. And now we have a whole bunch of periadjuvant trials that are going to give four doses. And then there is the whole question of how long to give the drug postoperatively. Any reflections on that? What would be your thoughts on how close we are to having figured that piece out?

Dr. Forde:
Yes, I think so as you mentioned Jon, it is a very rapidly evolving field, you know, and I think, so in clinical practice day-to-day, we have to revert back to the data we have available at that time. You know, we can look at and that is really phase 3 registrational studies. We can look at promising data from phase 2 trials like NADIM 2, for example. But extending that into our day-to-day practice is hard without showing in a randomized fashion in a large study that there is a benefit because it puts patients at risk of toxicity without clear benefits. So, my personal approach is to look at the eligibility of these trials, what sort of patients were enrolled, and all of them I think we should remember, enrolled sick patients. So, they all had ECOG performance status 0-1. The neoadjuvant trials, as I mentioned in one of the other episodes, have a pretty broad funnel. So, these are patients coming in the door with a lung mass, which is either larger than four centimeters or node positive and they have good performance status. But that is a broad category. Whereas in the adjuvant setting,

often you have to have a complete resection for the IMpower010 and the PEARLS trial and in some cases have started cisplatin based chemotherapy as an IMpower010. So, I think about those criteria. I agree completely with

Dr. Peters' thoughts in general that the strategies are probably more important, but I think in our day-to-day practice, we also have to keep in mind what type of patients receive these therapies. And that is what I discussed with patients and what happened when they received those therapies. You know, what toxicities did they have? How were their surgeries, if you are talking about neoadjuvant therapy. And I think that helps with our day-to-day practice in terms of our recommending to patients who are quite vulnerable and dependent on our opinion in terms of what we would do or suggest to happen for them, you know?

Dr. Spicer:
Yes. So now Dr. Peters, with a few different phase 3 options resulting both in neoadjuvant adjuvant. I have heard some people say that if they were to give chemo nivolumab to a patient with say, stage III and they were to have a response, they might then continue with adjuvant otelixizumab. Any thoughts about that? I mean, this is a question of sequencing. We were waiting on the periadjuvant data. In the meantime, is this a practice that you advocate for, that you think is reasonable?

Dr. Peters:
We are going to face a difficult time once we will be seeing coming this positive trial. I am sure there will be positive with perioperative immunotherapy. You will have these three induction cycles plus additional months of IO and you will find all these trials being positive. So, the question is, what is the added value of additional IO after surgery and who are the patients who benefit? And again, this is not the question of the trial, right? The trial is not trying to characterize or categorize the patients for additional IO. They are just a package, right, the whole strategy, yes, or no? So, we will try to invent a solution to this question, but we will not have evidence-based data. So, to me, would this trial read with slightly better hazard ratios than CHECKMATE-816? Or slightly, numerically, slightly better? We are in lung cancer, always working with this paradigm of probably more is better. So, I think that if this trial read with a kind of a signal for being slightly more beneficial, we might adopt, so sandwich, right? Some more immunotherapy afterwards. Is it correct or not? It can only be addressed in randomized trial, but this will be a very difficult trial to run, right.

Again, because in lung cancer we tend to think that more is better. Recommending a patient for less is very, very difficult in lung cancer, right? So, I would, I think we will face difficult kinds of questions. Maybe pulling all the data of the trials together and trying to look at surrogate biomarkers like circulating tumor with good technologies and new ones might be a way to try to create evidence from translational research on these trials. But it will need some additional years.

Dr. Spicer:
Dr. Peters, just to continue, since you are a lead on the PEARLS trial, one of the issues was the chemotherapy was sort of strongly recommended, but optional, and they did not seem to be much benefit to those patients who did not get chemo. We have mentioned a few of the other episodes, that sort of central pivotal importance of chemo with our current data. Any thoughts on that? We do not have any concurrent chemo IO adjuvant trials. Some criticisms of IMpower010 is that the initiation of otelixizumab took, well I think almost five months in a lot of cases. Could it be brought earlier? So, this question of timing in that space, any other thoughts on that?

Dr. Peters:
And just about this subgroup of PEARLS, these patients who did not receive adjuvant chemotherapy were not really extracting a benefit from IOs. That is what you quote. It is quite interesting because remember all these patients theoretically had an indication for adjuvant chemo. So, speaking about multiplicity of confounders, right. Who are these patients you who have in front of you, who have an indication for adjuvant chemo, and you decide with the patients not to go for what is indicated. They are probably very special patients, right. Not only the ones telling, "doctor I don't want it" because they accepted to be enrolled in a trial, but probably because they recover badly or with difficulty, they are weak, they have comorbidities, they had complications. And if I tell you these ones do not really benefit from adjuvant IO, well maybe it is self explained, right? They might also be the ones who do not continue IO or have by definition, a poor prognosis. So what I mean by that is we have to be very careful with subgroups. And the question of the role of chemo is not posed by this trial. Is not posed by adha, neither by the way. What is a standard is a standard and subgroups have been betraying us a little bit. So, I would not try to negotiate what is established. I would just try to understand how we can establish sustainable strategies for all patient in the future.

Dr. Spicer:
That is super interesting and I really the patient is at the center of all these decisions. And on that subject, Dr. Ford, any, any thoughts on, you know are there clearly patients who, who should not be assessed for either pre or postoperative immunotherapy? There is a lot of discussion about these borderline patients. Should they go to a pacific regiment or a new adjuvant or attempted surgery? So, some of your thoughts on that?

Dr. Forde:

Yes, I think that is an important thing as we translate clinical trial results into our day-to-day practice, you know, there are so we are still talking about at least 50% of patients in many of these trials are probably cured by the treatment in stage II disease at a very minimum are cured by surgery. So, what we are doing here, we are not, these are not patients who will die from cancer that 50%. So, what we do in the perioperative phase is trying to increase that number from 50 maybe to 60 or hopefully even higher, 70, 80 percent. And that is, I think we have to think about things like competing risks. So will some other condition this patient has, affect their lifespan in the near future. And if, for example, in one thing I think about five and 10 years, is lung cancer still the major threat to this patient's health? And if it is then, and they are otherwise healthy then I think perioperative therapy makes a lot of sense. On the other hand, if they have some major health condition which is going to affect their lifespan more approximately then I would lean against it. But I agree, John, it is, these are very complex discussions and, they are going to, I think we are going to spend even more time as these new trials emerge in terms of discussing them with our patients and their families.

Dr. Spicer:
Sounds like we might need a few more episodes. So, thank you very much for these thoughts. Obviously not solid data on all these questions, but we do have to practice in the absence of evidence for all of, for every question. And so thank you for your expert opinions on that. Okay. Thank you very much.

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