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Released: 11/30/2022
Valid until: 11/30/2023
Time needed to complete: 2h 36m

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Key Unmet Needs in Patients with Surgically Resectable NSCLC

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Dr. Forde:
Welcome to this episode where we are going to discuss some key unmet needs in the management of patients with surgically resectable early-stage lung cancer. And first of all, I am going to go to Dr. Tricia Cottrell, who is an immunopathologist, to discuss some of these considerations in more detail in terms of particularly eGFR and ALK testing for patients with newly diagnosed resectable lung cancer and how that impacts our care and how we can work that into our work schedules. Dr. Cottrell?

Dr. Cottrell:
Thank you. So obviously, we are in an exciting area, where we have next generation sequencing that can identify a handful of targetable mutations and some really exciting trial data to support using targeted therapies in that subset of patients. Clinically, you know, we have a challenge with trying to manage a very small pre-treatment biopsy and getting as much information as possible out of it as quickly as possible. Targeted assays can sometimes offer us a much quicker result but using panels for next generation sequencing can offer us a much broader set of data regarding the tumor's mutational status. So, I think it is a current challenge in the capacity of these labs to turn around molecular testing results quickly, is certainly a challenge. So, there is a balance between sort of an optimal workflow and a practical workflow. And in the setting where molecular data is not going to be available in a timely fashion for a surgically resectable patient, it is probably better to get that patient to surgery and find out whether or not they are eligible for these targeted therapies in the adjuvant setting. I would also add that an area of active investigation for pathology is validating pathologic response as an endpoint in these clinical trials. And we have some other episodes where I get into detail on that.

Dr. Forde:
Excellent. And Dr. Peters, you were one of the leaders of one of the major adjuvant trials recently, the PEARLS trial, which has just been published. Can you comment on that trial and potential indications for adjuvant pembrolizumab?

Dr. Peters:
Yes, thanks a lot. It was a trial led, of course, sponsored by the company, because of a very large size of the trial, but it was made by two collaborative groups in Europe, which was nice in terms of trying to define what makes sense as endpoints. They were TC and B etop and basically to trial down a kind of a standard in stage IB to stage IIIA. IB is more than four centimeters. And the idea was to try to find an event of disease-free survival, which would be across all the ITT population or as an alternative secondary dual co-primary endpoint only in high PD-L1. So, this trial was nice in the fact it was showing a benefit in disease free survival in the ITT population, so across strata of PD-L1 and in stage IB to stage IIIA. But when we were looking at the dedicated subgroup which was supposed to have the highest magnitude of benefit as seen in all trials in lung cancer, the high PD-L1, it was not found to be significantly beneficial in this specific subgroup. So very strange. ITT is positive, so it is a huge group, but the very dedicated one with the expectation of being the best for pembrolizumab was not. And just looking a little more deeper in this data of high PD-L1, it is quite reassuring to see that pembro

is performing better there. You have this incremental benefit of pembro by stratum of PD-L1, the highest, the best. But we had an unexpected and probably not explainable, I would say, overperformance of the standard arm, the control arm in this high PD-L1. We will probably never explain it. It is probably a combination of prognostic factors there, but it's not because of pembro. Pembro is reliably doing better, according to the strata of PD-L1. So, I think this trial can conclude of a benefit of pembro in stage IB to IIIA non-small cell lung cancer, regardless of PD-L1. I think it would be a fair statement there.

Dr. Forde:
And that was a placebo-controlled trial, was it? PEARLS?

Dr. Peters:
Absolutely, it was.

Dr. Forde:
Yes, so probably, in terms of design, the strongest of these three trials that we are talking about earlier, IMpower010, CheckMate 816, and PEARLS. Dr. Spicer, could you discuss some of the considerations? Which patients would you, for example, prefer adjuvant therapy? I think we have heard from Dr. Cottrell, those patients for whom, despite our best efforts, we cannot obtain eGFR results and non-squamous of course, but are there other patients for whom adjuvant therapy are appropriate and any other considerations and unmet needs, in particular, in early-stage lung cancer?

Dr. Spicer:
Yes, so you know, I think just starting from the recent data that Dr. Altorki presented the World Lung on stage IA, where we saw DFS only about 70% at five years from resection, whether it was a sublobar or a lobectomy, indicates to me, anyways, that we have issues with progression of disease, even in the earliest of operable stages. So, to me, it is clear that there is an unmet need in that regard, and we still have very little trial data in the IBs and IIAs, the no-negative patients. And even if you extend to the IIBs in CheckMate 816, it was a small proportion of the study. So, in terms of understanding neo-adjuvant versus adjuvant treatments in that context, we probably need quite a bit more data. I think that the biomarkers we have available to us post-resection for those who treated with upfront surgery are still clearly lacking in terms of understanding, you know, when to assign immunotherapy. We were seeing sort of conflicting results based on PD-L1. Is there something about the stage tumor microenvironment that we could better leverage, that maybe Dr. Cottrell could be giving us additional data to indicate which patients are going to do better with adjuvant IO as opposed to perhaps not offering that treatment which is kind of a long course of therapy with its own toxicities and whatnot? So, I think the decision tree in the adjuvant space, I think, remains quite complex. And you know, obviously I defer to you, my medical oncology colleagues, but we do need to be informed as surgeons as to how to discuss these path reports with our patients and help them be oriented to the conversations they will have with you, ultimately.

Dr. Forde:
Yeah and I think I would add that I think involving surgical colleagues in these trials at an early stage in design is very important in that often it is a major emotional and stressful event to undergo surgery and that becomes a very close bond. So, patients will often reach out to their surgeon and get guidance as well as their medical oncologist on how to approach the adjuvant setting. And that discussion can be guided by multiple people. Just to go back a little bit at the other adjuvant trial, Dr. Peters, at the IMpower010. So, say for example, both trials were available, both adjuvant therapies were available to you tomorrow, which would you consider? So, adjuvant atezolizumab or adjuvant pembrolizumab for a patient with stage II lung cancer?

Dr. Peters:
Yes, so the IMpower010 with atezolizumab, right, was asking really the same question with some differences as we said, as compared to PEARLS, but the same question about the role of adjuvant IO. The differences in IMpower010, the chemo was mandatory, some differences, right? But results and the statistical design of IMpower010 was one of this hierarchy, I would say a complex way to acknowledge and look at data, but basically showing again the benefits. But in IMpower010, the benefit was mainly seen in high PD-L1 expressors. And in Europe, that is where we have the registration only in more than 50% PD-L1. In some other countries like the U.S., like Japan, China, you have this chance of having potentially a larger way to prescribe in positive PD-L1.

So, I guess, of course, we need for the patients to follow what is registered, but I would not really bet that there are many differences between these drugs. So, I think patients with fully resecting non-small cell lung cancer, stage IB to stage III should be proposed adjuvant chemo and IO. The problem is what do you have in your hands, being reimbursed, available and accessible for the patient might be the main discriminants. And today it is atezolizumab, in our countries, in the adjuvant setting. If pembro comes in all commerce, it is not because it is more beneficial to me, just completes the picture of what you can really prescribe without fearing no reimbursement. So, I think it is going to be something more guided, unfortunately, by what you can really access to for your patients. I would probably suppose, maybe I am wrong, that the results are, I would say, equally showing a benefit.

Dr. Forde:
Yes. I think to go back briefly to Dr. Spicer, just those patients, so obviously we aim for optimal outcomes at all times, but real-life can be different and Dr. Cottrell, perhaps as well, but in those patients at surgery who have a microscopic positive margin, even macroscopic disease left behind, how do you approach those patients in terms of postoperative management?

Dr. Spicer:
So, this is really tough. I think it is important to remember that these adjuvant trials excluded all these patients with positive, whether microscopic or grossly positive margins. But they are the ones who have probably the worst outcome of the resected population, and it is not that infrequent. So, I think radiation has a role to play here, clearly. That probably needs a bit more investigation, but probably including these patients in future adjuvant trials and getting a better understanding of how to support them will be very important.

Dr. Forde:
Okay, well thank you all for joining me today and for joining us in this discussion. And there are several other episodes which address specific aspects of management of surgical lung cancer in this new era. Thanks again.

Announcer:
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