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Which Patients Should I Consider For Neoadjuvant or Adjuvant Immunotherapy?

Announcer:
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Dr. Forde:
Hello, this is Dr. Patrick Forde from Johns Hopkins University. This presentation is on, “Which Patients Should I Consider for Neoadjuvant or Adjuvant Immunotherapy?”. We know that unfortunately, the prognosis for patients with resected and non-small cell lung cancer is not good with 5-year survival for patients with stage IIA disease, only it is 60% and going down to 36% for those patients who have clinical stage IIIA, and this makes up quite a proportion of patients worldwide.

Approximately 500,000 people worldwide are diagnosed with potentially curable, surgically resectable lung cancer each year. When we talk about systemic therapy, we are mainly talking about those tumors which are 4 centimeters or greater and/or lymph node-positive, and in the latest edition of staging, the eighth edition, these would be clinical stage II and IIIA lung cancers.

In the CheckMate 816 trial, which looked at neoadjuvant chemo immunotherapy, the study enrolled patients with stage IB, 4 centimeters or greater to IIIA non-small cell lung cancer. Important to note that all of the current perioperative immunotherapy trials enrolled using the older seventh edition where stage IB cancers included 4 centimeters or greater tumors, and these were moved into stage II in the more recent eighth edition. All patients enrolled had an ECOG performance status for 0 to 1 and patients with known sensitizing EGFR mutations, or ALK alterations were excluded from the trial. So, I would not consider these patients for neoadjuvant or adjuvant immunotherapy at this point. Patients were stratified by stage, PD-L1 status, and sex and randomized to a control arm of chemotherapy and an investigational arm of chemotherapy plus nivolumab for three cycles. Surgery was planned within six weeks of the last treatment, and postoperatively, no further immunotherapy was delivered in CheckMate 816, and this is in contrast to some other phase 3 neoadjuvant chemo immunotherapy trials which are ongoing. Postoperative chemotherapy and/or radiation were permitted. Primary endpoints of the study were pathological complete response and event-free survival by a blind and independent review.

These are the baseline characteristics of the patients. So, when we are talking about which patients would potentially be eligible for this treatment, I think this is a relatively broad population and relatively representative of the patients we see in clinic. The majority of patients enrolled in this trial had stage IIIA, clinical stage IIIA disease. So definitely for that cohort of patients, I would consider neoadjuvant chemo immunotherapy, and we'd also see that this trial permitted patients to receive neoadjuvant carboplatin-based chemotherapy along with nivolumab. So, I think this trial doesn't necessarily require the use of cisplatin, which has practical implications for patients.

These are the event-free survival subgroup analysis from CheckMate 816. So, the overall trial did show a significant benefit favoring the addition of nivolumab to chemotherapy, and when we look across subgroups, nearly all did derive some benefit. We see a very significant benefit for those tumors which are stage IIIA, a hazard ratio of 0.54 favoring nivolumab plus chemotherapy, but also a benefit, particularly for non-squamous tumors or those tumors which are PD-L1-positive. I would not exclude, however, other patients from,

based on this analysis, and as you will see, most of these trend bars are favoring nivolumab plus chemotherapy. Now, let us move on to the other major perioperative study, which has been published in the last couple of years and has led to the approval of adjuvant immunotherapy. This was the IMpower010 trial, and this study enrolled patients with a completely resected stage IB, 4 centimeters or greater, to IIIA non-small cell lung cancer, again, using the older seventh edition. Patients at good performance status and all patients irrespective of PD-L1 were enrolled. Patients were stratified by sex, histology, stage of disease, and PD-L1 expression. Important to note that all patients in this trial had to receive cisplatin-based adjuvant chemotherapy.

After completion of chemotherapy, they were randomized to a control arm of best supportive care or to atezolizumab given once every three weeks for one year, and the primary endpoints of this study that were relatively complex, however, were tested hierarchically looking initially at PD-L1-positive tumors at 1% or above in the stage II and IIIA population. If that were positive, then the all-randomized stage II and IIIA population would be examined, and finally, if that were positive, the intention to treat population irrespective of PD-L1 would be assessed. And this trial did show a significant disease-free survival benefit favoring the use of adjuvant atezolizumab after cisplatin-based chemotherapy for those patients who have PD-L1-positive stage II and IIIA disease, and you will see this translates through to, at 3 years, about a 12% difference in disease-free survival favoring atezolizumab over best supportive care.

An important point to note with this study was that those patients who had PD-L1-negative tumors did not benefit from treatment, at least in terms of disease-free survival, and the FDA approval in the US is focused on those patients with PD-L1-positive cancers.

Drilling down in more detail on this group, a major part of the benefit was seen in those patients with PD-L1 high cancers with a hazard ratio of 0.43 favoring atezolizumab for this group. In the lower PD-L1 group 1 to 49%, the hazard ratio was not so significant at 0.87. So, I think it is very clear that patients with high PD-L1 benefit from adjuvant atezolizumab in the absence of EGFR and ALK. However, for lower PD-L1, I think it is more of a nuanced discussion where we discuss the risks and benefits of this treatment with patients.

So, to conclude, which patients should I consider for neoadjuvant or adjuvant immunotherapy? I think patients who have newly diagnosed clinical stage II or IIIA in the eighth edition, non-small cell lung cancer that is 4 centimeters are greater in diameter and/or node-positive and do not have EGFR or ALK alterations are all potential candidates for neoadjuvant chemotherapy plus nivolumab. I would particularly favor this for patients who have clinical stage IIIA disease or a node-positive disease in general, and also for those patients who do not wish to have a more prolonged course of adjuvant immunotherapy.

For those patients for whom surgery has been performed, adjuvant atezolizumab is approved for PD-L1-positive non-small cell lung cancer after adjuvant cisplatin-based chemotherapy, and I think this is important to note, patients should still receive adjuvant chemotherapy. And the greatest benefit is really seen in those high PD-L1 tumors of 50% and above. To mention briefly, there is a third trial, which we hopefully will see more results from soon, the PEARLS trial looking at adjuvant pembrolizumab, and this may be a future option agnostic to PD-L1 status. Thank you for attention.

Announcer:
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