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

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What Is the Evidence Supporting Neoadjuvant Immunotherapy in Early-Stage NSCLC?

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Dr. Forde:
Hello, my name is Patrick Forde, from Johns Hopkins University, and in this session I am going to discuss the evidence supporting neoadjuvant immunotherapy in early-stage non-small cell lung cancer.

Over the last several years, we have seen emerging data on single agent anti-PD-1 or PD-L1 and some studies also looking at combination CTLA-4 and PD-1 in the treatment of resectable non-small cell lung cancer. In the LCMC3 study, we saw the use of neoadjuvant atezolizumab prior to surgery for patients with resectable lung cancer, and this showed promising results in terms of major pathological response, and importantly also in terms of overall survival at up to three years follow up.

In the NEOSTAR trial on the right of this slide, you'll see again very promising outcomes at two and a half years from surgery, and many patients were still disease free, either from treatment with neoadjuvant nivolumab or nivolumab plus ipilimumab. In the NADIM trial, we saw the use of chemotherapy plus nivolumab for patients with resectable stage IIIA non-small cell lung cancer where they had mediastinal lymph node involvement. And we have longer term follow up on this study now, showing pathologic response rates in the 63% range, and at three to four years, more than 75% of patients were still alive even with stage IIIA lung cancer. On the right of your screen, you'll see another study looking atezolizumab plus chemotherapy, showing very similar promising results. And when we compare this to the historic pCR rate after neoadjuvant chemotherapy of 2 to 6%, both of these studies suggest a significantly increased clinical efficacy. In the CheckMate 816 trial, we examined patients with stage IB to IIIA non-small cell lung cancer using the seventh edition. So, one edition previous to the current, Patients had no known sensitizing EGFR or ALK alterations and were randomized to a control arm of chemotherapy given for three cycles prior to surgery or chemotherapy plus nivolumab. Patients underwent surgery within six weeks of the last treatment, and there was no mandated postoperative immunotherapy, so patients could receive further chemotherapy or radiation per the choice of the patient and the treating oncologist. The primary endpoints of the study were pCR and event-free survival by blinded independent review.

These were the baseline characteristics of the patients, well matched in both arms. About 64% of patients had stage IIIA non-small lung cancer, and about half the patients had non-squamous tumors. This was the disposition of the patients enrolled, and you'll see here is something we see with neoadjuvant trials in general. More patients will commence to therapy, and more patients will complete the planned therapy compared to when the therapy is given in the adjuvant setting. In this study, 94% and 85% respectively of the patients completed the planned neoadjuvant therapy, and 83% and 75% respectively had definitive surgery.

These are the adverse events and somewhat surprisingly though we were adding another drug, nivolumab, to chemotherapy, we did not see any significant increase in toxicity, which is encouraging. There were also very few treatment-related deaths in both arms, and none related to treatment in the nivolumab plus chemotherapy arm. In the first endpoint of this study, we saw a significant increase in

pathological complete response with the addition of nivolumab to chemotherapy. In the intention to treat population of all patients enrolled, this went from 2.2% with chemo alone to 24% with NIVO plus chemo. And similar deltas were seen when we looked at the patients who underwent resection and also looking only at the primary tumor.

The key other primary endpoint here was event-free survival, and this was the registrational endpoint. And this was reported as positive area this year with a hazard ratio of 0.63, favoring nivolumab plus chemotherapy, and approximately a 19% difference at two years in event-free survival, favoring nivolumab plus chemo. And this benefit was seen across enrolled subgroups. You'll see particular benefit for patients with PDL-1 positive tumor is in stage IIIA disease, but overall, nearly every subgroup derives some benefit from the addition of nivolumab to chemotherapy. We also saw some interesting findings in terms of the surgical outcomes. Fewer patients had required a pneumonectomy in the nivolumab plus chemotherapy arm, and historically a pneumonectomy has been associated with high morbidity and mortality, and more patients were able to have lobectomies or lung-sparing surgeries in the arm where patients receive nivolumab.

We also were able to look at the outcomes for patients whether they achieved a pathological complete response or not, and this is a potential early metric to predict how patients will do long term. And in this study, patients who had a pCR at the time of resection did extremely well. At two years, more than 90% of patients were event-free compared to about 50% among those patients who did not have a pathological complete response. So, this is potentially an early predictor of benefit, and you can imagine scenarios where this could be used for further triaging patients postoperatively to novel clinical trials or novel therapies.
And also, there was a promising early indicator of an overall survival benefit. This was the first pre-specified interim analysis, and at this interim analysis there was a very high bar for statistical positivity, but the trend favored nivolumab plus chemotherapy with a hazard ratio of 0.57 and approximately a 12% difference in overall survival at two years favoring nivolumab plus chemo.

These are several of the ongoing phase 3 neoadjuvant chemotherapy plus immunotherapy trials in resectable non-small cell lung cancer. We've seen that the Checkmate 816 trial has reported its primary results. We await primary results from the IMpower030 trial looking at atezolizumab plus chemotherapy in the neoadjuvant setting followed by adjuvant atezolizumab.

The 77T trial, which adds adjuvant nivolumab to neoadjuvant chemo-IO, and also in the KEYNOTE-671 trial, looking at neoadjuvant pembrolizumab, and the AEGEAN trial, looking at durvalumab, and all of these trials are expected to report out in the next few years. Finally, in conclusion, we know that the addition of anti-PD-1 to neoadjuvant chemotherapy does not increase toxicity and improves efficacy including surgical outcomes. The highest benefit in seen in PDL-1 positive and higher stage disease, however, in general benefit was seen across all enrolled patient subgroups. Thank you for your attention today.

Announcer:
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