Spotlight

Neoadjuvant therapy gains FDA approval in non-small cell lung cancer

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SUMMARY

Forde et al.1 reported on a randomized clinical trial (CheckMate 816) and showed that neoadjuvant therapy with nivolumab plus chemotherapy led to improved event-free survival and pathological complete response rate in patients with resectable non-small cell lung cancer (NSCLC).

Approximately 30% of patients with non-small cell lung cancer (NSCLC) present with resectable early-stage disease at the time of diagnosis; even with complete surgical resection, there is a significant risk of disease recurrence.7,3 The gains associated with use of perioperative chemotherapy have led to modest improvement in overall survival, though pathological complete responses are relatively uncommon (<5%).4,3 Either neoadjuvant or adjuvant platinum-based chemotherapy is considered standard therapy for early-stage NSCLC, with adjuvant approach being the most preferred among the two. The rationale for the use of the neoadjuvant approach includes the potential to eradicate micrometastatic disease earlier in the treatment course, increased initiation rate of systemic therapy, and assessment of pathologic response that could guide future treatment. Prior phase II studies showed that the use of neoadjuvant nivolumab5 or nivolumab plus chemotherapy6 led to promising results with respect to pathological complete response, survival, safety, and feasibility.

In this spotlight, we highlight the results of CheckMate 816, recently reported in the New England Journal of Medicine by Forde et al.1

In this randomized phase III study, patients with stage IB to IIIA NSCLC (according to the staging criteria of the AJCC, seventh edition) received nivolumab (360 mg), a PD-1 inhibitor, in combination with platinum-based chemotherapy or platinum-based chemotherapy alone for three cycles, followed by definitive surgery. Surgery was planned to occur within 6 weeks after the completion of neoadjuvant treatment. Of note, post-operative chemotherapy or radiation was optional.

The study met its primary endpoints of event-free survival (EFS) and pathological complete response (pCR defined as 0% viable tumor in resected lung and lymph nodes). The median EFS was 31.6 months with nivolumab plus chemotherapy and 20.8 months with chemotherapy alone (HR 0.63). Though the EFS across most key subgroups favored nivolumab plus chemotherapy, the magnitude of benefit was the most favorable for patients with stage IIIA disease, tumor PD-L1 expression level ≥1% and nonsquamous histology. The pCR rate was 24% and 2.2% for the two treatment arms, respectively (p < 0.001). At the first prespecified interim analysis, the overall survival rates were not reached for both arms (HR 0.57) and did not meet criteria for significance. Additional follow-up is needed.

Importantly, there were no detrimental effects on surgical outcomes. In the nivolumab plus chemotherapy group and in the chemotherapy-alone group, 83.2% and 75.4%, respectively, underwent definitive surgery. There were no differences in rates of delayed surgery, with low rates of surgery cancellation in both arms. The use of minimally invasive approaches was more common, and pneumonectomies were less common in the nivolumab plus chemotherapy group than in the chemotherapy alone group.

No unexpected safety signals were observed. The most common grade 3/4 treatment-related adverse events were neutropenia (8.5% with nivolumab plus chemotherapy and 11.9% with chemotherapy alone) and decreased neutrophil count (7.4% and 10.8%, respectively). The incidence of immune-mediated adverse events was low, and majority were grade 1/2.

In an exploratory analysis, analysis of ctDNA in 89 patients revealed that the percentage of patients with ctDNA clearance was higher with nivolumab plus chemotherapy than with chemotherapy alone.

On the strengths of these observations, the FDA has granted approval of this regimen, with use of chemoimmunotherapy regimen in the neoadjuvant setting for resectable lung cancer.

However, questions remain. Although pathological complete response may be a predictor of prolonged survival7 in solid tumors, the use of this endpoint is yet to be validated in the era of immunotherapy studies in lung cancer. The association of pathological complete response with survival benefit requires further evaluation.

Recent phase III trials investigating adjuvant therapies have also led to approvals with incorporation into clinical practice of osimertinib for patients with resected NSCLC whose tumor harbor an EGFR mutation8 and atezolizumab for patients with resected stage II-IIIA tumor with PD-L1 expression ≥1%,9 based on the ADAURA and Impower010 studies, respectively. The adjuvant approach may be easier to implement because adjuvant chemotherapy has been the preferred approach in the United States in many centers. Implementing the neoadjuvant strategy in clinical practice will have its challenges given the higher need for multidisciplinary...
coordination of care and earlier referral to medical oncology.

Finally, questions remain about optimal duration of perioperative therapy with immunotherapy combinations. Ongoing studies such as CheckMate 77T (NCT04025879) will address whether additional adjuvant immunotherapy will further improve EFS. The emerging tools to detect minimal residual disease using plasma ctDNA could identify patients at highest risk for recurrence and guide the use of additional therapy. In studies with post-operative immunotherapy, clinical benefit appears to be limited to patients with high PD-L1 expression; further evaluation of predictive biomarkers to personalize peri-operative therapy will lead to better overall outcomes.

In summary, these advances in the curative setting for patients with NSCLC are rapidly being incorporated into clinical practice; it is hoped that the improved EFS will translate into a higher cure rate with the addition of immunotherapy in the perioperative setting.

DECLARATION OF INTERESTS

S.S.R. is a part of the consultancy/advisory board for Amgen, BMS, Astra Zeneca, Merck, Lilly, Gennab, Eisai, and GSK and provides research support to institutions for Amgen, Astra Zeneca, BMS, Advaxis, Pfizer, Gennab, Merck, and GSK.

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