Immunotherapy Before and After Surgery Improves Lung Cancer Outcomes

Adding checkpoint inhibitors to chemotherapy before surgery and continuing them alone afterward reduces the risk of disease progression, recurrence and death.

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Immunotherapy, which has transformed the treatment of metastatic non-small-cell lung cancer (NSCLC), may also be a good option before and after surgery for people with earlier stages of disease, according to recent studies presented at the European Society for Medical Oncology (ESMO) Congress. Starting a checkpoint inhibitor prior to surgery can help shrink or even eliminate tumors, and using these drugs alone after surgery could let patients avoid side effects from prolonged chemotherapy.

Lung cancer has a high mortality rate, in part because it is often not detected until advanced stages. Around one third of patients diagnosed with NSCLC have resectable disease, meaning their tumors can be surgically removed. But the risk of recurrence after surgery is high without additional neoadjuvant (pre-surgery) or adjuvant (post-surgery) treatment, and chemotherapy alone has shown limited benefit.

Immune checkpoint inhibitors interfere with the interaction between the PD-1 receptor on T cells and its binding partner, known as PD-L1, on tumors. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block PD-1 or PD-L1 can release the brakes and restore T-cell activity. People with higher levels of PD-L1 on their tumors tend to respond better to this type of treatment.

As previously reported, the Food and Drug Administration (FDA) recently approved Keytruda (pembrolizumab), a PD-1 checkpoint inhibitor, as an immunotherapy option to be used before and after surgery for earlier-stage NSCLC. The approval was supported by data from the Phase III KEYNOTE-671 trial (NCT03425643), which enrolled people with previously untreated resectable Stage II, IIIA or IIIB NSCLC. They were randomly assigned to receive neoadjuvant treatment with Keytruda or a placebo plus platinum-based chemotherapy before tumor removal; afterward, they received adjuvant Keytruda or a placebo alone.

The Keytruda regimen led to significant improvements in event-free survival and overall survival.

The median event-free-survival time was 17.0 months in the placebo group but was not yet reached in the Keytruda group because a majority of patients had not yet experienced disease progression. The event-free survival rate at two years was 62% in the Keytruda group versus 41% in the placebo group, indicating a 42% reduction in the risk of disease progression, recurrence or death.

Likewise, the median overall survival time was 52.4 months in the placebo group but was not reached in the Keytruda group because a majority of patients were still alive, representing a 28% reduction in the risk of death. Keytruda recipients were nearly five times more likely to have a pathological complete response (18% versus 4%), meaning no remaining cancer in the removed tissue. Treatment was generally safe, though side effects were common in both groups.

Keytruda may soon have competition for this indication.

The Phase III CheckMate-77T trial (NCT04025879) evaluated another PD-1 checkpoint inhibitor, Opdivo (nivolumab), for pre- and post-surgery treatment, again in people with Stage IIA to IIIB NSCLC. The participants were randomly assigned to receive Opdivo or a placebo plus chemotherapy for four cycles before tumor removal, followed by adjuvant Opdivo or placebo alone.

The Opdivo regimen led to a statistically significant and clinically meaningful improvement in event-free survival, Tina Cascone, MD, PhD, of the University of Texas MD Anderson Cancer Center, reported at ESMO. Event-free survival time was 18.4 months in the placebo arm but was not reached in the Opdivo arm. Event-free survival rates at 18 months were 70% with Opdivo versus 50% with placebo, for a 42% lower risk of disease progression, recurrence or death. Here, too, the pathological complete response rate was five times higher in the perioperative Opdivo group (25% versus 5%). However, overall survival data are not yet mature in this study, and follow-up is ongoing.

People with ≥1% tumor PD-L1 expression saw a greater benefit, while those who received Opdivo before but not after surgery—for example, due to side effects—fared worse. Treatment was generally safe, and side effects were consistent with those seen in previous studies; 32% of patients in the Opdivo group and 25% in the placebo group experienced severe treatment-related adverse events.

“This study builds on the standard-of-care neoadjuvant treatment and supports perioperative nivolumab as an effective approach that reduces the risk of lung cancer relapse,” Cascone said in an MD Anderson news release. “These findings add to evidence that the perioperative immunotherapy path gives patients with operable lung cancer an opportunity to live longer without their cancer returning.”

Bristol-Myers Squibb plans to submit these data to the FDA for consideration of an expanded indication for perioperative treatment. Opdivo is currently approved for the treatment of metastatic NSCLC and for neoadjuvant treatment of resectable cancer in combination with chemotherapy before surgery, but not yet for post-surgery treatment.

Another presentation at ESMO reported long-term results from the Phase III CheckMate-816 trial (NCT02998528), which compared three cycles of Opdivo plus platinum-based chemotherapy versus chemotherapy alone before surgery—but without post-surgery immunotherapy—for patients with Stage IB to IIIA NSCLC.

After three years, adding Opdivo led to a sustained reduction in disease progression or death. People with ≥1% tumor PD-L1 expression saw a greater benefit. In that subgroup, three-year event-free survival rates were 72% with neoadjuvant Opdivo plus chemotherapy versus 47% with chemotherapy alone. Pathological complete response rates were 33% and 2%. For people with <1% PD-L1 expression, event-free survival rates were 42% and 39%, respectively.

Overall survival data remains immature but shows a promising trend. Among patients with ≥1% PD-L1 expression, the risk of death was 63% lower. Three-year survival rates were 85% with neoadjuvant Opdivo plus chemotherapy versus 66% with chemotherapy alone. People with <1% PD-L1 expression saw a smaller 19% reduction, with survival rates of 71% versus 60%, respectively.

"The three-year results with neoadjuvant nivolumab with chemotherapy are a continuation of the statistically significant and clinically meaningful results we have seen with this regimen in the treatment of resectable non-small-cell lung cancer, and they provide hope for patients that they may achieve long-term benefit," Mariano Provencio Pulla, MD, PhD, of Hospital Universitario Puerta de Hierro in Madrid, said in a news release.

Another Phase III trial dubbed AEGEAN (NCT03800134) tested Imfinzi (durvalumab), a PD-L1 checkpoint inhibitor, as perioperative treatment for Stage IIA to IIIB resectable NSCLC. Imfinzi is currently approved for metastatic or Stage III NSCLC that cannot be surgically removed.

The participants were randomly assigned to receive Imfinzi or a placebo plus platinum-based chemotherapy for four cycles prior to surgery, followed by adjuvant Imfinzi or a placebo alone for up to 12 cycles. Study results were previously reported at this year's American Association for Cancer Research annual meeting and recently published in The New England Journal of Medicine.

Again, event-free survival was significantly longer with Imfinzi. The median event-free survival time was 25.9 months in the placebo group but was not yet reached in the Imfinzi arm. After about a year of follow-up, event-free survival rates were 73% in the Imfinzi group, compared with 65% in the placebo group, representing a 32% reduction in the risk of disease progression, recurrence or death. Pathological complete response rates were 17% versus 4%, respectively.

"Throughout decades of research with adjuvant and neoadjuvant chemotherapy, we only succeeded in increasing cures by around 5%," principal investigator John Heymach, MD, PhD, of MD Anderson said in a news release. "This study shows that a combination of neoadjuvant and adjuvant durvalumab offers benefit for patients and may have the potential to change standard of care for patients with resectable non-small-cell lung cancer. Going forward, we face a series of questions about how to build more effective regimens without giving more treatment than is

necessary.”

Heymach and Cascone both noted that future studies are needed to determine which patients get the most benefit from neoadjuvant therapy and may be able to avoid further treatment and which ones remain at high risk for recurrence and may require additional therapy after surgery.

“Looking ahead,” said Cascone, “it will be critical to identify patient and disease characteristics that will tell us who can potentially be cured with neoadjuvant immunotherapy only and who will benefit from more intensified treatment strategies.”

Discussing the CheckMate-77T and KEYNOTE-671 findings at ESMO, Marina Garassino, MD, of the University of Chicago, said that while it is evident that checkpoint inhibitors before lung cancer surgery improve outcomes, the advantages of adjuvant immunotherapy after surgery are less clear. While further studies are underway, she recommended that neoadjuvant immunotherapy should be considered for all patients with resectable tumors but “the adjuvant part should be discussed on an individual patient-by-patient basis.”

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