FDA Approves Keytruda Immunotherapy for Operable Lung Cancer

The checkpoint inhibitor is now indicated for pre- and post-surgery treatment of Stage II or III non-small-cell lung cancer.

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On October 16, the Food and Drug Administration (FDA) approved Keytruda (pembrolizumab) as an immunotherapy option to be used before and after surgery for earlier-stage non-small-cell lung cancer (NSCLC).

Keytruda already had five previous FDA indications for NSCLC. The newest indication means the drug can now be used for neoadjuvant (presurgery) treatment along with platinum-based chemotherapy before surgical removal of lung tumors of at least four centimeters or with lymph node involvement, followed by adjuvant (post-surgery) treatment as a single drug. Starting medications prior to surgery can shrink tumors, potentially making them easier to remove. Using Keytruda alone after surgery enables patients to avoid side effects from prolonged chemotherapy.

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

The new approval is supported by data from the Phase III KEYNOTE-671 trial (NCT03425643), which evaluated neoadjuvant Keytruda plus chemotherapy followed by surgery and continued adjuvant treatment with Keytruda alone. The study enrolled 797 participants with a median age of 64 years who had previously untreated resectable Stage II, IIIA or IIIB NSCLC. Patients were eligible regardless of PD-L1 expression level; one third had high (at least 50%) PD-L1 expression.

The participants were randomly assigned to receive Keytruda or a placebo via IV infusion every three weeks plus chemotherapy (cisplatin with either pemetrexed or gemcitabine) for up to four cycles before surgery. After surgery, they received Keytruda or a placebo alone for 13 more cycles or until they experienced disease progression or unacceptable side effects. Tumor status was assessed every 16 weeks for the first three years, then every six months thereafter.

The Keytruda regimen led to statistically significant improvements in event-free survival and overall survival compared with neoadjuvant chemotherapy alone with no post-surgery medication.

As reported in The New England Journal of Medicine in August, the median event-free survival time was 17.0 months in the placebo group but not yet reached in the Keytruda group because a majority of participants 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, reflecting a 42% reduction in the risk of progression, recurrence or death. Keytruda recipients were nearly five times more likely to have a pathological complete response, or no evidence of remaining cancer (18% versus 4%).

Likewise, the median overall survival time was 52.4 months in the placebo group but not reached in the Keytruda group because a majority of patients were still alive, reflecting a 28% reduction in the risk of death, according to the FDA's approval announcement. These results will be presented at the upcoming European Society for Medical Oncology (ESMO) Congress.

[Update: See Merck's press release about the data presented at ESMO.]

Treatment was generally safe, though side effects were common: 45% of Keytruda recipients and 37% of placebo recipients reported severe (grade 3 or higher) treatment-related adverse events. Side effects were similar to those seen in people who use Keytruda plus chemotherapy or chemotherapy alone for other types of cancer, including nausea, fatigue, constipation, diarrhea, decreased appetite, cough, shortness of breath and low blood cell counts. One risk of checkpoint immunotherapy is that while it unleashes T-cell activity against cancer, it can also trigger excessive inflammation affecting organs throughout the body. If recognized promptly, these reactions can be managed by stopping Keytruda and treatment with corticosteroids.

"There remains a need for treatment options to improve outcomes for patients with earlier stages of non-small-cell lung cancer," lead trial investigator Heather Wakelee, MD, of Stanford University, said in a Merck press release. "This important milestone has the potential to change the current treatment paradigm for resectable NSCLC that is greater than four centimeters or has lymph node involvement by offering an immunotherapy-based regimen that has demonstrated statistically significant improvements in overall survival and event-free survival compared to a placebo and chemotherapy regimen."

Click here for full prescribing information for Keytruda.

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