# Immunotherapy Post-Surgery Improves Overall Survival for Kidney Cancer

Patients who used adjuvant Keytruda had a reduced risk of recurrence and a 38% lower risk of death.

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For the first time in fifty years, results from a Phase 3 randomized, placebo-controlled trial have shown an overall survival benefit from an adjuvant therapy in patients with kidney cancer.

Treatment with pembrolizumab [Keytruda], an immunotherapy drug, after surgery significantly prolonged overall survival in patients with clear-cell renal-cell carcinoma (ccRCC) at high risk for recurrence, according to an analysis of results from the KEYNOTE-564 study. Pembrolizumab was associated with a 38% reduction in risk of death compared with placebo.

“We can now tell our patients that pembrolizumab after surgery not only delays recurrences but also helps them live longer,” said the study’s lead investigator Toni Choueiri, MD, of Dana-Farber Cancer Institute.

Choueiri, director of the Lank Center for Genitourinary Oncology at Dana-Farber, presented the findings at the American Society of Clinical Oncology (ASCO) Genitourinary Cancer Symposium on January 27, 2024.

The KEYNOTE-564 trial was designed to evaluate adjuvant pembrolizumab following nephrectomy (removal of the cancerous kidney) within 12 weeks prior to randomization. The double-blind, Phase 3 study, carried out at hundreds of sites internationally, enrolled 994 patients who were randomized to pembrolizumab once every three weeks for about a year, or a placebo.

Pembrolizumab targets a molecular pathway that cancer cells commandeer to evade attack by the body’s immune system. By blocking this “checkpoint” pathway, the drug helps free the immune system’s army of T cells to combat tumors.

For inclusion in the trial, patients had to have a clear-cell component to their tumor and be at intermediate or high risk of recurrence. Some patients with resected metastases after nephrectomy were also eligible. For patients with ccRCC, surgery is intended to be curative. However, between 30% and 50% of patients can experience recurrence after surgery. Recurrences often result in metastatic disease, which is usually incurable.

Investigators have been trying to find ways to reduce recurrences and prolong survival for this patient group since 1973, the date of the first randomized controlled trial of an adjuvant therapy. An adjuvant therapy is a medicine intended to enhance efficacy after primary treatment of the cancer, which in this case is surgery.

“Since 1973, more than 12,000 patients with kidney cancer participated in adjuvant studies versus a control arm and none of the studies showed the experimental arm extends lives until now with the KEYNOTE-564 study,” says Choueiri. “We showed pembrolizumab extends survival. It doesn’t only delay recurrence.”

In the first interim analysis of the KEYNOTE-564 study, Choueiri and colleagues reported that adjuvant pembrolizumab improved disease-free survival in patients with kidney cancer at high risk of relapse. Pembrolizumab was approved in 2021 as adjuvant treatment for patients with kidney cancer based on these KEYNOTE-564 results.

This third interim analysis was completed after a median of 57.2 months of follow up. Adjuvant pembrolizumab significantly prolonged overall survival versus placebo in trial participants. Overall survival benefits with pembrolizumab were consistent across subgroups, irrespective of stage, risk stratification, immunological biomarkers, and other characteristics.

Approximately 18% of patients stopped therapy due to side effects associated with pembrolizumab. No treatment related deaths were reported with pembrolizumab. The investigators reported previously that adjuvant pembrolizumab did not result in clinically meaningful deterioration of health-related quality of life.

Prior to the approval of pembrolizumab, there was no widespread accepted standard of care for patients with ccRCC after treatment with surgery. Now, with adjuvant pembrolizumab as standard of care for this patient group, Choueiri and colleagues are investigating whether it can be improved by combining pembrolizumab with the HIF-2 inhibitor belzutifan.

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