Checkpoint Immunotherapy Combos Reduce Kidney Cancer Progression

Bavencio or Keytruda plus targeted therapy slowed disease progression in Phase III studies.

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Combinations of immunotherapy and targeted therapy reduced the risk of disease progression or death in people with advanced renal cell carcinoma, the most common type of kidney cancer, according to recent study findings.

Results presented at the European Society for Medical Oncology (ESMO) 2018 Congress this month in Munich showed that the checkpoint inhibitor Bavencio (avelumab) plus the tyrosine kinase inhibitor Inlyta (axitinib) slowed cancer progression compared with the current standard of care in people with advanced kidney cancer.

Right before the ESMO meeting, Merck & Company announced that its checkpoint blocker Keytruda (pembrolizumab) plus Inlyta led to improvements in both progression-free survival and overall survival.

Renal cell carcinoma (RCC) accounts for around 9 out of 10 cases of liver cancer. About 63,300 people will be diagnosed with kidney cancer and nearly 15,000 will die from it this year, according to the American Cancer Society. It has few symptoms during its early stages, and at the time of diagnosis, many patients already have metastatic disease that has spread beyond the kidney.

Kidney cancer generally does not respond well to chemotherapy or radiation therapy. The first-line standard of care for advanced RCC is surgery followed by targeted therapies, such as Sutent (sunitinib) or Nexavar (sorafenib), that block tyrosine kinases involved in cell growth and blood vessel development. Inlyta, a next-generation tyrosine kinase inhibitor with fewer side effects, is currently approved for second-line therapy after a prior treatment failure.

Bavencio and Keytruda are monoclonal antibodies that help the immune system fight cancer. They interfere with PD-1, a checkpoint receptor on T cells that plays a role in regulating immune function. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block the interaction between PD-1 and PD-L1, its binding partner on tumor cells and immune cells in tumors, can release the brakes and restore T-cell activity.

Approved for several types of cancer, Keytruda blocks PD-1. Bavencio, which is approved for

advanced bladder cancer and metastatic Merkel cell carcinoma, blocks PD-L1. Another PD-1 blocker, Opdivo (nivolumab), is currently approved for advanced kidney cancer, with or without Yervoy (ipilimumab), which blocks a different checkpoint known as CTLA-4.

Today's immunotherapies don't work for everyone or for all types of cancer. People with higher PD-L1 levels in their tumors tend to do better on checkpoint inhibitors, but this is not a reliable predictor of individual response. These drugs work best against so-called hot tumors that have many mutations to attract T cells. Combining checkpoint blockers with targeted therapy may help them to work better.

Bavencio Plus Inlyta

Robert Motzer, MD, of Memorial Sloan Kettering Cancer Center in New York, presented results from JAVELIN Renal 101, a Phase III trial evaluating Bavencio plus Inlyta for people with advanced clear cell renal cell carcinoma who were being treated for the first time.

The study enrolled 866 participants, including 21 percent with favorable risk, 62 percent with intermediate risk and 16 percent with poor risk for disease progression. Nearly two thirds (63 percent) had PD-L1 positive tumors, meaning PD-L1 expression on at least 1 percent of immune cells.

Half the participants were randomly assigned to receive Bavencio by IV infusion every two weeks plus twice-daily oral Bavencio, while the rest received once-daily oral Sutent on a schedule of four weeks on and two weeks off.

Overall, the median progression-free survival (PFS), meaning patients were still alive without worsening of disease, was 13.8 months in the Bavencio/Inlyta group compared with 8.4 months in the Sutent group. Among those with PD-L1 positive tumors, the median PFS was 13.8 months and 7.2 months, respectively. Both differences were statistically significant, meaning they probably were not attributable to chance.

The immunotherapy regimen performed better in all prognostic risk categories and across PD-L1 levels. Overall survival data are not yet mature because a majority of participants are still alive, and follow-up is ongoing.

The overall response rate, meaning complete or partial tumor shrinkage, was twice as high with Bavencio/Inlyta, both overall (51.4 percent versus 25.7 percent) and in the PD-L1 positive subgroup (55.2 percent versus 25.5 percent). Four people in the combination therapy group achieved complete responses.

Treatment was generally safe, but side effects were common. About 71 percent in both groups experienced severe adverse events, according to the study abstract. Motzer reported that 4 percent of Bavencio/Inlyta recipients and 7 percent of Sutent recipients stopped treatment because of side effects. Diarrhea was the most frequently reported severe side effect.

Immune-related side effects are a concern with checkpoint inhibitors. In addition to restoring

immune responses against cancer, they can also take the brakes off the immune system more broadly, leading to excessive inflammation of healthy tissue including the lungs, colon and endocrine glands. The most common immune-mediated event in this study was hypothyroidism.

“The findings support the potential of avelumab plus axitinib as a new treatment approach for patients with advanced RCC,” Motzer said in an ESMO press release. “[Tyrosine kinase inhibitors] and checkpoint blockers like avelumab both may have potential immune-modulating functions that, when combined, may provide clinical benefit in patients with advanced RCC that exceeds the effects of the respective drugs alone, without compromising toxicity.”

Pfizer and Merck KGaA (a smaller German company), which are jointly developing the combination, previewed the data in a September press release, stating that these are the first positive Phase III data for immunotherapy plus a tyrosine kinase inhibitor to be reported for any type of cancer.

Keytruda Plus Inlyta

In the lead-up to the ESMO meeting, Merck & Company issued a press release announcing results from the Phase III KEYNOTE-426 trial, which evaluated Keytruda plus Inlyta in a similar population of 861 patients with previously untreated advanced RCC.

These top-line results were released several months ahead of schedule, indicating that the combination showed benefits sooner than expected. Merck did not provide detailed numbers, and these results have not yet been presented at a scientific conference or published in a medical journal.

The company announced that the study met its primary endpoints of improved progression-free survival and overall survival in people randomly assigned to Keytruda/Inlyta compared with those who used Sutent. Overall response rates also favored the combination. Benefits were seen across prognostic risk groups and PD-L1 levels.

“Keytruda, in combination with the tyrosine kinase inhibitor Inlyta, resulted in significant and clinically meaningful improvements in overall survival, progression-free survival and objective response in this Phase III study,” said Merck Research Laboratories president Roger Perlmutter, MD, PhD. “This marks the first time that combination treatment with an anti–PD-1 therapy has achieved the dual primary endpoints of overall survival and progression-free survival as first-line therapy in advanced renal cell carcinoma.”

Both Pfizer/Merck KGaA and Merck & Company indicated that they plan to submit their latest data to the Food and Drug Administration for approval of a new indication for first-line kidney cancer treatment.

Click here to see the ESMO 2018 program.

Click here for full prescribing information for Bavencio.

Click here for full prescribing information for Keytruda.