# Checkpoint Combos Improve Advanced Kidney Cancer Outcomes

Keytruda and Bavencio may soon join Opdivo/Yervoy as first-line treatment options for advanced renal cell carcinoma.

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Three immunotherapy combinations reduce the risk of disease progression or death in people starting initial treatment for advanced clear cell renal cell carcinoma, according to late-stage study results presented at the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium last week in San Francisco.

As reported in advance of the conference, the PD-1 checkpoint inhibitor Keytruda (pembrolizumab) plus the targeted therapy Inlyta (axitinib) led to improvements in both progression-free survival and overall survival compared with the standard therapy Sutent (sunitinib). Researchers also presented follow-up data from studies of the other approved PD-1 blocker, Opdivo (nivolumab), and the PD-L1 inhibitor Bavencio (avelumab).

Nearly 74,000 people will be diagnosed with kidney cancer this year, according to the American Cancer Society. Renal cell carcinoma (RCC) accounts for more than 90 percent of these cases, and among those with RCC, about 70 percent have clear cell cancer. Kidney cancer often has few symptoms during its early stages, and many patients already have metastatic disease that has spread beyond the kidney at the time of diagnosis.

PD-1 is a checkpoint receptor on T cells that helps regulate immune function. 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, PD-L1, can release the brakes and restore T-cell activity. A higher level of PD-L1 in tumors is associated with better response in many studies but it does not predict individual outcomes.

The PD-1/PD-L1 approach works only if T cells can get into tumors, however. Combining these drugs with other types of therapy could help immune cells reach, recognize and attack cancer cells. In these studies, Keytruda and Bavencio were evaluated in combination with Inlyta, a VEGFR tyrosine kinase inhibitor that interferes with blood vessel development. Opdivo was combined with Yervoy (ipilimumab), which blocks a different checkpoint, known as CTLA-4, that suppresses T-cell activity.

Keytruda Plus Inlyta

KEYNOTE-426, presented at the conference by Thomas Powles, MD, of Barts Cancer Institute in London and published in The New England Journal of Medicine, evaluated Keytruda plus Inlyta versus Sutent in 861 people with previously untreated metastatic clear cell RCC. Sutent is a targeted therapy that inhibits VEGFR and other tyrosine kinase enzymes.

People assigned to the Keytruda/Inlyta regimen had improved progression-free survival compared with Sutent (patients were alive without worsening disease for a median 15.1 versus 11.1 months), a higher overall response rate (complete or partial tumor shrinkage in 59 percent versus 36 percent) and a higher complete response rate (full tumor remission in 5.8 percent versus 1.9 percent). Responses were seen in people with PD-L1-positive and PD-L1-negative tumors.

After a year on treatment, overall survival rates were 90 percent for those taking Keytruda/Inlyta versus 78 percent for those taking Sutent—a 47 percent reduction in the risk of death.

Treatment was generally safe, but side effects were common. In both groups, about 60 percent experienced severe (grade 3 or higher) treatment-related adverse events, although treatment discontinuation because of side effects was uncommon (8 percent with Keytruda/Inlyta versus 10 percent with Sutent).

Bavencio Plus Inlyta

At the same conference session, Toni Choueiri, MD, of the Dana-Farber Cancer Institute in Boston presented follow-up results from the JAVELIN Renal 101 trial, which compared Bavencio plus Inlyta versus Sutent in 886 people with advanced RCC, about two thirds of whom had PD-L1-positive tumors. These results were also published in The New England Journal of Medicine.

The main results, presented at the European Society for Medical Oncology conference last October, showed that the median progression-free survival was 13.8 months in the Bavencio/Inlyta group compared with 8.4 months in the Sutent group (a 31 percent risk reduction). Among those with PD-L1-positive tumors, the corresponding medians were 13.8 months and 7.2 months, respectively (a 39 percent reduction).

The overall response rate was twice as high with Bavencio/Inlyta, both in the full study population (51 percent versus 26 percent) and in the PD-L1-positive subgroup (55 percent versus 26 percent). This was also the case for complete response rates (3.4 percent versus 1.8 percent for the full population; 4.4 percent versus 2.1 percent for the PD-L1-positive group). In this study, overall survival data are not yet mature because a majority of participants are still alive.

Choueiri presented further details about response rates in various subgroups, showing that Bavencio/Inlyta outperformed Sutent in all prognostic risk categories. Progression-free survival was longer with the immunotherapy combination in people with poor risk (median 6.0 versus 2.9 months), intermediate risk (8.4 versus 13.8 months) and favorable risk (13.8 months versus not yet reached). Overall response rates were also better in all risk groups.

The mean duration of response was more than four months longer in the Bavencio/Inlyta group. About 20 percent of people in the Bavencio/Inlyta arm and 40 percent in the Sutent arm went on to receive follow-up treatment with various immune-based or targeted therapies. In theory, first-line treatment could change the biology of the disease and influence subsequent treatment, Choueiri said. In the full study population, the time to progression on the subsequent therapy or death—known as PFS2—was 18.4 months in the Sutent group but not reached in the Bavencio/Inlyta group because a majority had not yet progressed.

Here, too, treatment was safe but side effects were common. About 70 percent in both treatment arms experienced severe adverse events; about 8 percent of patients who took Bavencio/Inlyta and 13 percent of those who used Sutent stopped treatment for this reason.

Opdivo Plus Yervoy

Finally, Nizar Tannir, MD, of MD Anderson Cancer Center in Houston, presented long-term follow-up results from CheckMate-214, evaluating Opdivo plus low-dose Yervoy versus Sutent. This combination is already approved as first-line therapy for people with immediate or poor risk of disease progression, while Opdivo alone is approved for patients previously treated with tyrosine kinase inhibitors.

CheckMate-214 included 1,096 people with previously untreated advanced RCC; about three fourths were classified as intermediate or poor risk.

As previously reported, after about two years of follow-up, the median overall survival for intermediate/poor risk patients was 26.0 months with Sutent but not yet reached in Opdivo/Yervoy group. The 12-month overall survival rates were 80 percent with Opdivo/Yervoy and 72 percent with Sutent, falling to 75 percent and 60 percent, respectively, at 18 months. Overall response rates were 42 percent (including 9 percent complete responses) with Opdivo/Yervoy and 27 percent (including 1 percent complete responses) with Sutent.

Longer-term follow-up results at 30 months continue to show an advantage for the checkpoint combination. The median overall survival in the intermediate/poor risk group was 26.6 months with Sutent but was still not reached in the Opdivo/Yervoy arm. The 30-month overall survival rates were 60 percent versus 47 percent, respectively.

Overall response rates in the intermediate/poor risk group were 42 percent (including 11 percent complete responses) with Opdivo/Yervoy and 29 percent (with just 1 percent complete responses) with Sutent. The immunotherapy responses were durable, with more than half lasting 18 months or longer. Although the Opdivo/Yervoy response rates were similar for intermediate/poor and favorable risk patients, Sutent worked better in the latter group and outperformed the checkpoint combo.

Although people taking Opdivo/Yervoy were less likely to experience severe adverse events than those taking Sutent (46 percent versus 63 percent), more patients in the former group discontinued treatment because of side effects (22 percent versus 12 percent, respectively).

## Which Combo Is Best?

Powles and Choueiri both suggested that the immunotherapy combinations they studied represent a new standard of care for people with advanced kidney cancer. While all three checkpoint regimens worked better than Sutent, it is not yet clear which of them is best.

Lori Wood, MD, of Dalhousie University in Halifax, Canada, compared results from the three studies at the conference, as did Bernard Escudier, MD, of Gustave Roussy Cancer Campus in Villejuif, France, in an editorial in The New England Journal of Medicine. Importantly, these data are not directly comparable because the study populations are not the same, with different proportions of patients with intermediate/poor progression risk and PD-L1-positive tumors.

Overall response rates with Keytruda/Inlyta or Bavencio/Inlyta (59 percent and 51 percent) were a bit higher than the 42 percent response rate with Opdivo/Yervoy. However, the complete response rate was highest with Opdivo/Yervoy (5.8 percent, 3.4 percent and 11 percent, respectively). Keytruda/Inlyta worked well regardless of PD-L1 levels, while the other combos were more effective in people with PD-L1-positive tumors. Unlike the other two regimens, Bavencio/Inlyta does not yet have mature overall survival data. And more people taking Opdivo/Yervoy stopped treatment because of side effects.

Treatment cost is also be a factor when weighing the regimens. In addition to drug prices, this should also take into account differences in the time patients must spend receiving therapy and the amount of time and effort required from doctors and nurses, Wood said. Sutent and other targeted therapies require fewer medical visits and side effects can often be managed by phone, while immunotherapy requires more frequent monitoring and more urgent management of adverse events.

Clinicians and people with kidney cancer may soon be able to weigh these options in the real world. Keytruda and Bavencio, both in combination with Inlyta, have each received a Food and Drug Administration priority review designation and decisions are expected in June.

“What we’re doing in advanced kidney cancers is pushing the envelope,” Choueiri said. “These treatments may not be curative, but patients are living longer, and the disease is becoming more chronic.”

Click here to read the KEYNOTE-426 study abstract.

Click here to read the JAVELIN Renal 101 study abstract.

Click here to read the CheckMate-214 study abstract.

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