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'Unprecedented' 73% Response Rate With Combo in Untreated RCC

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SAN FRANCISCO — The combination of an immunotherapy and a vascular endothelial growth factor (VEGF) inhibitor resulted in a groundbreaking response rate in metastatic renal cell carcinoma (RCC), according to results of an ongoing phase 1b study.

In a cohort of treatment-naive patients, 38 of 52 (73%) achieved an objective response, including 4 complete responses, with the combination of axitinib (*Inlyta*, Pfizer) plus pembrolizumab (*Keytruda*, Merck).

The study details were presented here at the Genitourinary Cancers Symposium (GUCS) 2018 and simultaneously published online February 10 in the *Lancet Oncology*.

The response rate was called "unprecedented" by the study authors, led by Michael Atkins, MD, from Georgetown-Lombardi Comprehensive Cancer Center in Washington, DC.

Median progression-free survival (PFS) was 20.9 months. Among responders, median duration of response was 18.6 months. Overall survival data were not mature.

This is uncharted territory, said Sumanta Pal, MD, a urologic oncologist at City of Hope Cancer Center in Duarte, California, who acted as meeting discussant: "An 18.6-month median duration of response and a median PFS of 21 months, this is unprecedented."

Median follow-up in the trial was 17.6 months.

"The regimen was highly active," Atkins told the meeting audience.

"The antitumor activity of the combination is superior to that expected from axitinib or PD-1/PD-L1 [programmed cell death-1/programmed cell death ligand-1] pathway inhibitor monotherapy," he said. The combination roughly doubled the efficacy of the drugs when used alone.

"We think this combination could present a major advance in the treatment of this disease as well as help define effective combinations of similar drugs for other cancers," Atkins said in a press statement.

Previous Combos Were Toxic

In advanced RCC, treatment with various VEGF pathway inhibitors has "rarely" resulted in durable and complete responses, note the authors. "The standard first-line drugs sunitinib and pazopanib lead to a median progression free survival of around 8–12 months," they write.

The idea of combining anti-VEGF agents with immunotherapy is not new; previous research also showed efficacy. However, excessive toxicity caused investigators and developers to abandon the approach.

Axitinib is a newer, "more selective" VEGF receptor inhibitor than sunitinib and pazopanib, which are multitargeted tyrosine kinase inhibitors (TKIs) that have been tested in this setting. "Many of these toxicities were related to off-target effects of these multitargeted TKIs," Atkins said about the older drugs.

Axitinib is already approved for second-line treatment of advanced RCC. Pembrolizumab is approved for use in many cancer types, but not RCC

(nivolumab is the only immunotherapy approved for RCC).

The team reports that the new combination of axitinib and pembrolizumab was "tolerable."

This outcome "contrasts with the toxicities reported in other clinical trials" combining checkpoint inhibitors with other TKIs of the VEGF pathway, the authors add.

For the combination of axitinib with pembrolizumab, the team reports that grade 3 or worse treatment-related adverse events occurred in 34 (65%) patients. The most common were hypertension (12 patients [23%]), diarrhea (5 patients [10%]), fatigue (5 patients [10%]), and increased alanine aminotransferase concentration (4 patients [8%]).

The most common possibly-immune-related adverse events included diarrhea

(15 patients [29%]), increased alanine aminotransferase (9 patients [17%]) or aspartate aminotransferase (7 patients [13%]) concentration, hypothyroidism (7 patients [13%]), and fatigue (6 patients [12%]).

A total of 28 (54%) patients had treatment-related serious adverse events. The most common serious adverse events included diarrhea (6 patients [12%]), dyspnea (4 patients [8%]), and colitis (3 patients [6%]).

Overall, the adverse events reported "seem to be largely related to axitinib" say the investigators. Notably, 27 patients (about half) discontinued both treatments. The most common reasons for discontinuing both study treatments were adverse events (10 patients) and disease progression (9 patients).

The patients in this study had more favorable prognoses than in typical RCC trials, the authors commented. They note that "very few" patients had poor-risk disease per the Metastatic Database Consortium criteria; 46% of patients had favorable-risk disease and 44% had intermediate-risk disease. All participants also had previously undergone nephrectomy.

The investigators enrolled 11 patients to the dose-finding phase and later enrolled another 41 patients to the dose-expansion phase.

All participants received the same dose and schedule. Axitinib 5 mg was administered orally twice daily, with pembrolizumab 2 mg/kg administered intravenously every 3 weeks. Tumors were assessed (according to RECIST version 1.1) at baseline, at week 12, and then every 6 weeks.

On the basis of the results of this phase 1b trial, the US Food and Drug Administration granted the axitinib–pembrolizumab combination a breakthrough status.

A randomized phase 3 trial (NCT0285331) comparing the new combination to sunitinib monotherapy in the first-line setting is underway.

That trial, known as KEYNOTE-426, is evaluating whether axitinib and pembrolizumab will work better as a sequential treatment. This is an important difference because it would cost less. Both drugs are administered for shorter dosing periods when given as monotherapies than when given in combination. The patient population is also "less heavily selected" than that of the current study.

The study was funded by Pfizer. *Atkins has financial relationship with Pfizer and multiple other pharmaceutical companies. Pal has financial ties to Eisai, Ipsen, Astellas, Medivation, Bristol-Myers Squibb, Exelixis, Genentech, Myriad Pharmaceuticals, Aveo, Novartis, and Pfizer.*

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