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Checkpoint Inhibitors Produce Durable Responses in Metastatic RCC

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News

CHICAGO (FRONTLINE MEDICAL NEWS) – A combination of two immune checkpoint inhibitors – ipilimumab and nivolumab – produced durable responses in patients with metastatic renal cell carcinoma in a phase I trial (http://abstracts.asco.org/144/AbstView_144_129458.html).

At 40.1 weeks of follow-up, the median duration of response for patients treated with nivolumab 3 mg/kg and ipilimumab (Yervoy) 1 mg/kg for four cycles followed by nivolumab maintenance was 31weeks, and for patients treated with nivolumab 1 mg/kg/ and ipilimumab 3 mg/kg the median duration of response had not been reached, reported Dr. Hans J. Hammers of the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore.

“The objective response rate suggests greater activity than reported previously with nivolumab or ipilimumab monotherapy,” Dr. Hammers said at the annual meeting of the American Society of Clinical Oncology.

“Responses appear durable even after discontinuation of study drug,” he added.

Nonredundant checkpoints

Both drugs are monoclonal antibodies directed against receptors in immune system checkpoints. Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor that acts as an early brake point in the immune response; nivolumab is a programmed cell death-1 (PD-1) inhibitor that serves as a late brake. By releasing the brakes, the drugs allow the immune system to operate full throttle against cancer.

Ipilimumab is approved by the Food and Drug Administration for the treatment of metastatic melanoma. Nivolumab is an investigational agent that has been shown to have good antitumor activity in monotherapy against melanoma and other malignancies.

At ASCO 2014, investigators reported that the combinations (http://www.oncologypractice.com/oncologyreport/news/conference-news/asco-annual-meeting/single-article/video-drug-combo-delivers-unprecedented-metastatic-melanoma-survival/ab0ad3b849da577ecde1cb3cc91da813.html) resulted in “unprecedented” 2-year overall survival rates for patients with metastatic melanoma.

Dr. Hammers and his colleagues investigated the combination in a phase I trial comparing two different combinations of the checkpoint inhibitors.

Patients with untreated or previously treated metastatic renal cell carcinoma (mRCC) with clear-cell histology were randomly assigned to receive intravenous induction therapy every 3 weeks for four cycles with either nivolumab 3 mg/kg and ipilimumab 1 mg/kg (N3/I1) or nivolumab 1 mg/kg and ipilimumab 3 mg/kg (N1/I3). Patients received two infusions during each induction, with nivolumab first, followed by ipilimumab started at

least 30 minutes after completion of the nivolumab infusion.

Following induction, all patients went on to continuous nivolumab 3 mg/kg every 2 weeks until disease progression.

Adverse events

Treatment-related adverse events, the primary endpoint, occurred in 16 of the 21 patients (76.2%) assigned to N3/I1) and in all 23 patients assigned to N1/I3. Grade 3 or 4 adverse events occurred in 5 of 21 (23.8%) and 14 of 23 (60.9%), respectively. There were no treatment-related deaths.

The grade 3 or 4 adverse events included diarrhea in one patient in N3/I1 and eight patients in N1/I3, increased lipase in three and six patients, respectively, and increased amylase in one and three patients. There were no other grade 3 or 4 adverse events in either study arm. In addition, there were no high-grade pulmonary adverse events or cases of pneumonitis, which are often seen with immunotherapy, Dr. Hammers noted.

The confirmed objective response rate (ORR) was 43% (9 of 21) in N3/I1 and 48% (11 of 23) in N1/I3. As noted before, the median duration of response was 31.1 weeks in N3/I1 and not reached in N1/I3.

Of the patients who had objective response, the responses were ongoing at last follow-up in 7 of 9 on N3/I1 and 9 of 11 on N1/I3.

There was only one complete response, however, occurring in a patient who received N1/I3. Partial responses occurred in nine patients on N3/I1 and 10 in N1/I3.

The respective progression-free survival rates at 24 weeks were 65% and 64%, which “compares favorably with the nivolumab monotherapy experience,” Dr. Hammers said.

The majority of patients in each study arm had significant reductions in tumor burden of the target lesions, he added.

Of the patients with ongoing responses, 3 of 9 in the N3/I1 arm and 5 of 11 in the N1/I3 arm continued to have responses after discontinuing therapy for reasons other than disease progression.

“This encouraging antitumor activity reported with this combination is the basis for a planned phase III combination trial in the first-line setting for the treatment of metastatic renal cell carcinoma patients,” Dr. Hammers said.

‘Gutsy move’

Dr. Primo Lara, professor of medicine at the University of California, Davis, who was the invited discussant, commented that, “at least for now, I think we could say that combination checkpoint blockade in RCC is at least additive, recalling that the single-agent response rate in this disease for nivo[lumab] is about 20%-29%, and for ipi[limumab] is about 13%, and some of these responses are encouragingly durable.”

He cautioned, however, that the toxicities with the combined drugs, primarily driven by ipilimumab, “are not inconsequential.”

"We heard today that a phase III trial has been initiated, presumably with a lower-dose ipi[limumab] arm, but I think that's really a gutsy move, considering that there were only 21 patients in that subset of patients that led to this phase III decision. Just a fair warning to everyone that toxicities observed in a phase I trial tend to magnify in a larger phase III when you have more centers, different eligibility criteria, and less experienced folks administering a pretty toxic combination," he said.

The study was funded by Bristol-Myers Squibb and Ono Pharmaceutical. Dr. Hammers has received research funding from BMS. Dr. Lara disclosed serving as a consultant/advisor, and receiving honoraria and research funding from many companies, but not BMS.
