Metastatic HCC: Activity for First Time Shown in Second-Line Treatment

BY ED SUSMAN

SAN FRANCISCO—For the first-time, a second-line treatment for metastatic hepatocellular carcinoma, using the investigative small molecule inhibitor palbociclib, appears to show a benefit in progression-free survival, according to Phase II data reported here at the Gastrointestinal Cancers Symposium (***Abstract 277***).

"Palbociclib demonstrates activity in patients with hepatocellular cancer after failure of first-line sorafenib," said Susan Littman, MD, Director of the GI Oncology Clinic of Kimmel Cancer Center of Thomas Jefferson University in Philadelphia.

"The duration of stable disease was 24 weeks among the 19 patients evaluable," she said in an interview at her poster. "There has never been a drug that has shown activity as a second-line treatment in patients with advanced liver cancer. All the studies have failed to demonstrate any positive results.

"Obviously we have to do another trial with more patients. I want to do a molecular analysis to see what the differences are between people who stay on the treatment and never progress and the patients who stay on the study and develop progressive disease."

At the meeting, which is co-sponsored by the American Gastroenterological Association Institute, American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology, Littman reported that three of the 19 patients had disease progression while they were being treated with palbociclib. Response Evaluation Criteria in Solid Tumors (RECIST) and levels of alpha-fetoprotein were used to determine tumor response. She said the stable disease achieved by most of the patients was consistent with cytostatic activity of small molecule inhibitors.

"There are a couple of people who have not progressed even though they have been off the study drug for as long as 17 months," she said, adding that four of the 19 patients remain alive and have stopped taking palbociclib.

"These types of responses are not seen in second-line liver cancer treatment. There is something in this drug that has perturbed things in the normal course of this disease to the point when you have these long-term survivors."

She said that some people had stable disease while on the drug—previously named PD-0332991—for 25 weeks and then suddenly progressed and that there were others who stayed on the drug but died of their underlying end-stage liver disease caused by cirrhosis. "But they had no progression of their cancer. That was really an unexpected finding."

She explained that palbociclib is an orally available, selective inhibitor of cyclin-dependent kinase 4/6, a key regulator of cell growth, and that preclinical data have shown inhibition of tumor cell lines and in animal xenograft models.

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Two Types of Responses

In patients, there are basically two types of responses, Littman said: (1) a "more traditional" cancer response of stable disease that then progresses; and (2) stable disease that remained stable, but then the underlying disease kills the patient. In this case, the cause of death in eight patients was end-stage liver disease, and in eight patients the cause of death was listed as hepatocellular cancer. One patient died of cholangiocarcinoma; and six patients remain alive—two of whom are still on the study, Littman reported.

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For the study, she and her colleagues recruited patients who had undergone surgery or stereotactic radiosurgery at least four weeks prior to enrollment and who had baseline magnetic resonance imaging or computer-assisted tomography scans that showed no evidence of active intracranial disease. The patients also were required to be off steroids for at least a week prior to study enrollment.

The researchers enrolled adults with hepatocellular carcinoma that had been refractory to currently available therapies, and who had been determined to have non-resectable disease by a multidisciplinary evaluation. The tumor biopsy had to exhibit serum alpha-fetoprotein levels of at least 200 micrograms per liter of blood and stain positive for the retinoblastoma function. Patients had to be evaluated in Child's-Pugh class A or B and ECOG Performance Status of 2 or less.

Patients who received previous radiotherapy or locoregional or systemic therapy were eligible, but a minimum interval of four weeks since the last anti-cancer treatment of any kind was required.

"Everybody in this study had advanced disease, and a few patients had metastases within the liver, which is common in this disease," Littman said.

No Standard-of-Care Options for Second-Line Metastatic HCC

Asked for his perspective, Tony Philip, MD, an attending physician at North

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PALBOCICLIB

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Shore-Long Island Jewish Cancer Institute, said: "We really have no standard-of-care options for second-line metastatic hepatocellular cancer, so the fact that the researchers are seeing an extended progression-free survival is encouraging."

He noted that although liver cancer is relatively rare in the United States, it remains a major cancer in the developing world.

"This study requires that the patients' tumors stain positive for the retinoblastoma gene, which I think is going to limit the usefulness of the drug, because the activity we see may be limited to a subset of hepatocellular patients."

Philip also noted that, of course, this is a Phase II trial, and that further research with the treatment in a randomized Phase III clinical trial will be required.

Study Details

In Littman's open-label, non-randomized study, the median age of the patients was 62; 20 of the patients were men and three were women; 12 patients were Caucasian, seven were Asian, and four were African-American.

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Their liver disease etiology was hepatitis C in nine; hepatitis B in five patients; alcohol-related cirrhosis in five patients, non-alcoholic steatohepatitis in one patient, and the cause of the other three patients remained unknown.

In six patients, the metastases were confined to the liver; in one patient the only site of metastasis was to the bone. All the other patients had metastases to at least two organs—most often to the lung, peritoneum, bones, or lymph nodes.

All of the patients had been treated with sorafenib for as few as two weeks or for as long as 104 weeks before becoming intolerant of the drug or their disease progressed despite being on sorafenib. Patients were treated with palbociclib 125 mg capsules orally once daily, administered on days 1 to 21 of a 28-day cycle, in repeated cycles.

One patient achieved a partial response with palbociclib, 14 patients had stable disease, three had progressive disease, and evaluation was not possible for four patients. One patient had progressive cholangiocarcinoma and probably had stable hepatocellular carcinoma, Littman said. That person died from the cholangiocarcinoma.

"Hepatocellular carcinoma is the fifth most common cancer worldwide and the third most frequent cause of cancer-related mortality," she noted. "To date, surgical resection and liver transplantation are considered the main curative treatment options. However, the majority of patients present with advanced tumor stage and poor liver function, rendering the patient ineligible for surgical interventions."

Littman noted that although patients with advanced pancreatic cancer are usually treated with sorafenib, response rates are typically unfortunately low with only modest benefits overall, and moreover, the toxicity profile of the drug limits treatment for many patients.

Next Steps

Littman said she is planning further studies, including one in which palbociclib monotherapy is compared with another agent plus palbociclib. The drug, which is being developed by Pfizer, is also being tested in breast cancer, stomach cancer, sarcomas, and other solid tumors. To date, palbociclib remains investigational and is not approved for any condition anywhere in the world, she added.

"When I design the follow-up to this study I will have to design it differently to take into account that we can stop the cancer completely, but that patients still die of underlying disease. We may have to make the endpoint cancer-related survival so we have a useful way of looking at it."