Keytruda Leads to Durable Response for Some People With Advanced Liver Cancer

Immunotherapy had a low response rate, but most responders continue to do well.

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About 16 percent of liver cancer patients who used the PD-1 checkpoint inhibitor Keytruda (pembrolizumab) after prior treatment with Nexavar (sorafenib) experienced tumor shrinkage, which in most cases lasted at least six months, according to findings presented at the 2018 Gastrointestinal Cancers Symposium (GI18) last week in San Francisco.

The median progression-free survival—meaning patients were still alive with no worsening of disease—was 4.8 months, representing an improvement over standard therapy for this difficult to treat cancer.

Hepatocellular carcinoma (HCC) is a type of liver cancer that can develop after long-term chronic hepatitis B or C infection, heavy alcohol use, fatty liver disease or other causes of liver injury. HCC is often diagnosed at a late stage and is hard to treat. Early-stage liver cancer may be treated with surgery or local chemotherapy; Nexavar is standard first-line therapy for more advanced HCC.

Andrew Zhu, MD, PhD, of Massachusetts General Hospital in Boston presented findings from Merck's Phase II KEYNOTE 224 study, which evaluated Keytruda in people with advanced HCC who had already used Nexavar.

Keytruda is a monoclonal antibody that blocks the PD-1 receptor (an immune checkpoint) on T cells, the main soldiers of the immune system. PD-1 plays a role in regulating immune function. Some tumors can hijack PD-1 to turn off immune responses against them, and drugs like Keytruda can release the brakes and restore T-cell activity.

KEYNOTE 224 included 104 advanced liver cancer patients who either had disease progression while taking Nexavar or were unable to tolerate it. More than 80 percent were men and the median age was 68. About 20 percent had hepatitis B and nearly 30 percent had hepatitis C. Almost all had compensated liver disease (Child-Pugh Class A). Two thirds had cancer that had metastasized, or spread beyond the liver.

Everyone in this open-label study received Keytruda by IV infusion every three weeks for up to two years, or until they experienced disease progression or intolerable side effects.

After a median follow-up period of about 8 months, the overall response rate—meaning complete or partial tumor shrinkage—was 16.3 percent. Only one patient had a complete response. In addition, 45.2 percent had stable disease, resulting in a combined disease control rate of 61.5 percent. Response rates were similar for people who had hepatitis B, hepatitis C or neither virus.

Looking further at the 17 responders, the median duration of response was 8.2 months, and 94 percent had responses lasting at least six months. At the time of the data analysis, 13 responders remained on treatment and still responding.

Looking at all patients, the median progression-free survival was 4.8 months, with 43.1 percent still alive without disease progression at 6 months. The median overall survival could not be determined because a majority of patients (77.9 percent) were still living.

Treatment with Keytruda was generally safe and well tolerated. Side effects were common but mostly mild or moderate. Seven people stopped treatment due to adverse events. The most frequently reported adverse events were pruritus, or itching (21.2 percent), fatigue (12.5 percent), diarrhea (9.6 percent) and AST liver enzyme elevation (9.6 percent).

The major concern with checkpoint inhibitors like Keytruda is immune-related side effects. These drugs work by restoring immune responses against cancer cells, but they can also take the brakes off the immune system more broadly, leading to inflammation of healthy tissue. Three people in this study experienced immune-mediated liver inflammation.

A Phase III randomized clinical trial known as KEYNOTE 240 is now under way, testing Keytruda versus a placebo as second-line treatment for people with HCC. If results continue to look promising, that study could support Food and Drug Administration (FDA) approval of the drug for liver cancer. Keytruda is currently approved for non-small-cell lung cancer, bladder cancer, head and neck cancer, melanoma and Hodgkin lymphoma.

As reported at the recent Liver Meeting, another PD-1 checkpoint inhibitor, Bristol-Myers Squibb's Opdivo (nivolumab), produced a similar stable disease rate in the CheckMate 040 trial, leading to its recent FDA approval for the treatment of people with HCC who previously used Nexavar.

Click here to read the GI18 abstract.

Click here to read Merck's press release about the study.
