FDA Approves Immunotherapy Combination for Liver Cancer

A third of patients treated with Opdivo plus Yervoy experienced complete or partial tumor remission.

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On March 10, the Food and Drug Administration (FDA) approved a combination of the checkpoint inhibitors Opdivo (nivolumab) and Yervoy (ipilimumab) for people with advanced hepatocellular carcinoma (HCC), the most common type of liver cancer.

The accelerated approval was based on results from the Phase I/II CheckMate 040 trial, which showed a response rate of 33% among HCC patients previously treated with Nexavar (sorafenib).

Over years or decades, chronic hepatitis B or C, heavy alcohol use, fatty liver disease and other causes can lead to development of cirrhosis and hepatocellular carcinoma. Liver cancer is often detected late and is difficult to treat, as it does not respond well to traditional chemotherapy. The tyrosine kinase inhibitor Nexavar is a standard first-line treatment for advanced liver cancer, but it doesn't work for many patients and most experience disease progression.

Opdivo is a PD-1 checkpoint inhibitor that helps the immune system fight cancer. PD-1, a receptor on T cells, 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, known as PD-L1, can release the brakes and restore T-cell activity. Opdivo was approved as a stand-alone treatment for HCC in 2017. Yervoy is a different type of checkpoint inhibitor that blocks CTLA-4, which turns off immune responses by suppressing T-cell replication.

Approval of the combination was based on results from the Phase I/II CheckMate 040 trial, which evaluated Opdivo alone and in various combinations in people with advanced HCC who had previously taken or could not tolerate Nexavar.

Participants were randomly assigned to receive different doses of Opdivo plus Yervoy, continuing treatment until they experienced disease progression or unacceptable side effects. A total of 49 people received the regimen approved by the FDA: 1 milligram per kilogram of Opdivo plus 3 mg/kg of Yervoy given by IV infusion every three weeks for four cycles, followed by 240 mg of Opdivo every two weeks.

Among people receiving this regimen, the overall response rate—meaning complete or partial tumor shrinkage—was 33%. Four patients (8%) experienced complete remission and twelve (24%) had partial responses. Most responses (88%) lasted at least six months, 56% lasted at least 12 months and 31% lasted at least two years.

At last year's Liver Meeting, researchers reported that people treated with this regimen had a median overall survival of 22.8 months. The 12-month overall survival rate was 61% and the 24-month survival rate was 48%.

Treatment with Opdivo and Yervoy was generally safe, though side effects were common. More than half (59%) experienced serious adverse reactions, and 29% stopped treatment for this reason, according to manufacturer Bristol-Myers Squibb. The most frequently reported adverse events were rash, itching, musculoskeletal pain, diarrhea, cough, decreased appetite, fatigue and fever.

The major concern with checkpoint inhibitors is immune-related adverse events, which are more common when these drugs are combined. Immunotherapy works by restoring immune responses against cancer cells, but it can also activate the immune system more broadly, harming healthy tissue. Liver inflammation was the most common severe immune-mediated side effect, followed by skin rash, endocrine problems, lung inflammation and colon inflammation. In most cases, these side effects could with a short course of corticosteroids.

The FDA granted accelerated approval based overall response rate and duration of response. Continued approval may be contingent upon verification of clinical benefit in later-stage trials.

A Phase III clinical trial, CheckMate 9DW, is now evaluating Opdivo plus Yervoy versus Nexavar or Lenvima (lenvatinib) as first-line treatment for advanced HCC. At the recent American Society of Clinical Oncology Gastrointestinal Cancers Symposium, researchers reported that a triple combination of Opdivo, Yervoy and the kinase inhibitor Cabometyx (cabozantinib) led to a higher response rate than the dual regimen.

"HCC is an aggressive disease in need of different treatment approaches," lead study investigator Anthony El-Khoueiry, MD, of the Keck School of Medicine at the University of Southern California said in a Bristol-Myers Squibb press release. "The overall response rate observed in the Opdivo plus Yervoy cohort of the CheckMate-040 trial underscores the potential of this dual immunotherapy as a possible treatment option for patients."

Click here for full prescribing information for Opdivo.

Click here for full prescribing information for Yervoy.

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