Immunotherapy Improves Survival for People With Liver Cancer

Three checkpoint inhibitors reduce the risk of death for patients with hard-to-treat liver and biliary tract cancers.

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A combination of two immune checkpoint inhibitors, Imfinzi (durvalumab) and tremelimumab, led to improved overall survival for people with advanced liver cancer, while Imfinzi plus chemotherapy prolonged survival for those with biliary tract cancer, according to studies to be presented this week at the 2022 ASCO Gastrointestinal Cancers Symposium. Another trial showed that Keytruda (pembrolizumab) also improved survival for liver cancer patients.

Over time, chronic hepatitis B or hepatitis C, fatty liver disease, heavy alcohol use and other causes of liver injury can lead to the development of hepatocellular carcinoma (HCC), the most common type of liver cancer. HCC is often detected late and is difficult to treat. Biliary tract cancer, which originates in the bile ducts (cholangiocarcinoma) or gallbladder, is also hard to treat.

HIMALAYA Trial

Ghassan Abou-Alfa, MD, of Memorial Sloan Kettering Cancer Center, and colleagues conducted the Phase III HIMALAYA trial (NCT03298451) to evaluate a single dose of tremelimumab added to Imfinzi for the treatment of advanced liver cancer.

Imfinzi is a monoclonal antibody that blocks the PD-L1 protein on cancer cells. PD-1 is an immune checkpoint protein on T cells that 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 PD-L1, its binding partner, release the brakes and restore T-cell activity. Tremelimumab, not yet approved by the Food and Drug Administration (FDA), blocks CTLA-4, a different checkpoint protein that suppresses T-cell multiplication. Another immune checkpoint combo—the PD-1 inhibitor Opdivo (nivolumab) plus the CTLA-4 inhibitor Yervoy (ipilimumab)—is currently approved for liver cancer.

This open-label international trial included 1,171 people with Stage III or IV inoperable HCC who had not used prior systemic therapies and were not eligible for local therapies. Such patients have a five-year survival rate of just 7%. The participants were randomly assigned to receive a single priming dose of tremelimumab plus Imfinzi administered by IV infusion every four weeks (known

as the STRIDE regimen), Imfinzi alone or the oral targeted therapy Nexavar (sorafenib).

Tremelimumab plus Imfinzi led to a significant improvement in overall survival compared with Nexavar, while Imfinzi alone was noninferior, meaning it worked at least as well as Nexavar. Patients treated with the STRIDE regimen had a 22% lower risk of death than those who received Nexavar. The median overall survival times were 16.4 months for the STRIDE regimen, 16.6 months for Imfinzi alone and 13.8 months for Nexavar. At two years, 41% of STRIDE recipients, 40% of Imfinzi monotherapy recipients and 33% of Nexavar recipients were still alive. At three years, the overall survival rates were 31%, 25% and 20%, respectively. However, progression-free survival, meaning patients were alive without worsening of disease, was not statistically superior with the combination or Imfinzi alone compared with Nexavar.

In addition, the Imfinzi combination demonstrated a higher overall response rate (20%), or likelihood of tumor shrinkage, than Imfinzi alone (17%) or Nexavar (5%), and it had a longer duration of response (22.3, 16.8 and 18.4 months, respectively).

The STRIDE regimen was generally safe, but it led to more side effects and treatment-related deaths than Imfinzi alone. Rates of severe (Grade 3 or 4) side effects were 26% with STRIDE, 13% with Imfinzi monotherapy and 37% with Nexavar. But fewer patients who received the combination or Imfinzi alone stopped treatment due to side effects compared with Nexavar recipients (8%, 4% and 11%, respectively).

Based on these findings, the STRIDE regimen could become a new first-line standard of care for inoperable HCC, the researchers suggested.

“Patients with unresectable liver cancer face a dismal prognosis, and new treatment options are critical to improving long-term survival,” Abou-Alfa said in an AstraZeneca press release. “The three-year overall survival rate and favorable safety profile seen with the STRIDE regimen set a new benchmark in this setting and underscore the potential of this innovative treatment approach.”

The researchers plan to look at whether outcomes differ based on the cause of liver cancer (for example, hepatitis B or C) as well as quality-of-life outcomes, according to Abou-Alfa.

TOPAZ-1 Trial

Another international Phase III trial, TOPAZ-1 (NCT03875235), evaluated Imfinzi plus chemotherapy for first-line treatment of advanced biliary tract cancer.

This study included 685 participants with previously untreated, inoperable advanced or metastatic gallbladder cancer (25%) or cholangiocarcinoma within (55%) or outside the liver (19%). They were randomly assigned to receive Imfinzi, administered every three weeks for up to three cycles and then every four weeks, or a placebo with standard-of-care IV chemotherapy (gemcitabine plus cisplatin).

An interim analysis showed that patients treated with Imfinzi plus chemotherapy had a 20% reduction in mortality compared with those who received chemotherapy alone. Although the difference in median overall survival time was small—12.8 months versus 11.5 months—the proportion of patients who were still alive at two years was greater with the combination than with chemotherapy alone (25% versus 10%). What's more, Imfinzi plus chemotherapy led to a 25% reduction in the risk of disease progression or death. Median progression-free survival times were 7.2 months versus 5.7 months, respectively. The combination also had a higher overall response rate (27% versus 19%).

Treatment with the Imfinzi combination was generally safe and did not lead to more side effects than chemotherapy alone. Rates of severe treatment-related adverse events were similar in the two treatment groups (63% versus 65%, respectively), as were rates of discontinuation due to adverse events (9% versus 11%), suggesting that most side effects were attributable to the chemotherapy. The most common adverse events were anemia, neutropenia (low white blood cells) and nausea.

"After minimal progress for more than a decade in advanced biliary tract cancer, the TOPAZ-1 results are a tremendous advance for our patients, showing a clear survival benefit for Imfinzi added to chemotherapy compared to standard of care with a remarkable safety profile," principal investigator Do-Youn Oh, MD, PhD, of Seoul National University College of Medicine in South Korea, said in an AstraZeneca press release. "This combination will provide a desperately needed and potentially practice-changing new treatment option in a setting where the current prognosis is devastating."

"TOPAZ-1 is the first Phase III trial to demonstrate the benefit of immunotherapy for improved overall survival [for inoperable biliary tract cancer], in combination with chemotherapy, creating a new standard of care," Cathy Eng, MD, of Vanderbilt-Ingram Cancer Center, commented in an ASCO press release. "Patients have a greater reason for hope given the positive results seen with the use of immunotherapy in biliary tract cancers."

KEYNOTE-394 Trial

Finally, a third Phase III study, KEYNOTE-394 (NCT03062358), evaluated Keytruda, a PD-1 checkpoint inhibitor as a second-line treatment for advanced liver cancer.

This indication received accelerated approval based on overall response data, but such medications are required to undergo further testing to confirm that they provide clinical benefits, such as improved survival, with longer follow-up. This was one of several immunotherapy indications reviewed at an FDA advisory committee meeting in April 2021 to decide whether they should remain in effect. The advisors voted unanimously to maintain the indication pending results from KEYNOTE-394.

This trial enrolled 453 patients in Asia who had advanced HCC previously treated with Nexavar or platinum-based chemotherapy. They were randomly assigned to receive Keytruda, administered by IV infusion every three weeks for up to two years, or a placebo plus the best supportive care

(for example, pain management).

Keytruda recipients saw a statistically significant improvement in overall survival, with a 21% reduction in the risk of death compared with supportive care alone, according to a Merck press release. The median overall survival time was 14.6 months in the Keytruda group versus 13.0 months in the placebo group. At two years, 34% of Keytruda recipients and 25% of placebo recipients were still alive. Keytruda also reduced the risk of disease progression or death by 26%, with median progress-free survival times of 2.6 months and 2.3 months, respectively. The overall response rate with Keytruda was 13%, compared with just 1% in the placebo group, and the duration of response was 23.9 months versus 5.6 months.

Treatment with Keytruda was generally safe and well tolerated. Rates of treatment-related severe adverse events were 14% in the Keytruda group and 6% in the placebo group. Therapies that unleash the immune system can lead to excessive inflammation that harms healthy tissue; 18% of Keytruda recipients experienced immune-mediated adverse events (3% of them severe), but so did 11% of placebo recipients.

“Hepatocellular carcinoma is a leading cause of cancer death across the world, and there are limited treatment options shown to extend survival for patients following treatment with sorafenib,” principal investigator Shukui Qin, MD, of Nanjing University of Chinese Medicine, said in the press release. “These overall survival data are very encouraging for patients with HCC previously treated with sorafenib and show the potential of Keytruda to extend the lives of these patients.”

Click here to read the HIMALAYA abstract (abstract 379).

Click here to read the TOPAZ-1 abstract (abstract 378)

Click here to read the KEYNOTE-394 abstract (abstract 383).

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