Tibsovo Could Be First Targeted Therapy for Cholangiocarcinoma

IDH1 inhibitor delayed progression of this often aggressive cancer of the bile ducts.

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The IDH1 inhibitor Tibsovo (ivosidenib), currently approved as a treatment for a type of leukemia, also appears to be effective against cholangiocarcinoma with a specific genetic mutation, according to research presented at the recent European Society for Medical Oncology Congress (ESMO 2019) in Barcelona.

Tibsovo nearly doubled progression-free survival time, from a median of 1.4 to 2.7 months, meaning people randomly assigned to receive the drug were still alive without disease progression about twice as long as placebo recipients. Experts said the results could potentially change standard practice.

“What we see in this study is really unprecedented,” Chris Verslype, MD, of University Hospital Leuven in Belgium, commented in an ESMO press release. “We previously had no options for patients with cholangiocarcinoma who failed systemic therapy, and they had very limited survival…. There is a gain in progression-free survival with ivosidenib that is clinically relevant for this patient population.”

Cholangiocarcinoma is a rare cancer of the bile ducts within or outside the liver. Bile, a fluid that helps digest fats, is produced by the liver and transported through bile ducts to the gallbladder for storage. If detected early, bile duct tumors can sometimes be surgically removed, but more often, the cancer is diagnosed at later stages. Cholangiocarcinoma may be treated with chemotherapy, but there are currently no approved targeted therapies. Advanced cholangiocarcinoma often progresses rapidly and has a high mortality rate.

Ghassan Abou-Alfa, MD, of Memorial Sloan-Kettering Cancer Center in New York City, presented findings from the ClarIDHy study, an international Phase III trial comparing Tibsovo versus placebo for people with advanced cholangiocarcinoma.

Tibsovo, from Agios Pharmaceuticals, targets cancer with a genetic mutation that encodes an abnormal version of IDH1 (isocitrate dehydrogenase-1), an enzyme that plays a role in cellular metabolism. This leads to the production of a cancer-causing metabolite known as D-2-hydroxyglutarate. Around 15% to 20% of people with cholangiocarcinoma have this mutation.

Tibsovo is currently approved for the treatment of relapsed or refractory acute myeloid leukemia with an IDH1 mutation.

This study included 185 people with previously treated inoperable or metastatic cholangiocarcinoma with IDH1 mutations. Two thirds were women, and the median age was 62. More than 90% had cancer that originated in bile ducts within the liver and had spread elsewhere in the body. Just over 40% had tried at least two prior therapies.

Participants were randomly assigned to take Tibsovo tablets or a matching placebo once daily. People in the placebo arm who experienced disease progression could cross over to the Tibsovo arm, and more than half did so.

The overall response rate was low in both groups (2% versus 0%), but people taking Tibsovo were more likely to have stable disease without further progression (51% versus 28%).

Study participants who received Tibsovo had significantly improved progression-free survival (PFS) compared with placebo recipients. At six months, 32% of Tibsovo recipients were still alive without worsening of their disease, compared with none of the placebo recipients; the PFS rate at 12 months was 22% versus zero. The median PFS duration was 2.7 months versus 1.4 months, respectively, representing a 63% reduction in the risk of disease progression or death.

The results also showed a trend toward longer overall survival with Tibsovo, but this was not statistically significant, meaning the difference could have been driven by chance. At six months, 67% of Tibsovo recipients and 59% of placebo recipients were still living. At 12 months, the survival rates were 48% and 38%, respectively. The median overall survival duration was 10.8 months in the Tibsovo group and 9.7 months in the placebo group.

However, because 57% of the people who progressed in the placebo arm crossed over to Tibsovo, they experienced some benefit too, reducing the difference between the two groups. While allowing such crossover is ethically the right approach and helps the greatest number of patients, it makes it harder to see an overall survival advantage. The researchers did a mathematical adjustment to account for crossover (known as rank-preserving structural failure time), estimating that the overall survival duration would otherwise have been six months in the placebo group, which was significantly shorter, and the survival rate would have been 46%.

Treatment was generally safe, but side effects were common. The most frequently reported adverse events were nausea, diarrhea and fatigue. Severe (Grade 3 or higher) adverse events occurred in 46% of participants in the Tibsovo group and 36% of those in the placebo group; the most common severe event was ascites (abdominal fluid accumulation). Fewer people taking Tibsovo stopped treatment because of adverse events (6% versus 9%).

“The ClarIDHy study demonstrates for the first time the feasibility and clinical benefit of targeting a molecularly defined subgroup in cholangiocarcinoma. It shows that targeting mutated IDH1 with ivosidenib significantly improves progression-free survival and gives a favorable trend in overall survival in patients with advanced IDH1-mutated cholangiocarcinoma,” Abou-Alfa concluded.

“The findings mean all patients with cholangiocarcinoma should be tested for IDH1 mutation,” he continued. “Tumor mutation profiling should be a new standard for the care for patients with this heterogeneous tumor type.”

Commenting on the findings for ESMO, Angela Lamarca, MD, of Christie NHS Foundation Trust, said, “The reported median progression-free survival may seem short, and some people may question whether this is clinically meaningful. However, for researchers working in cholangiocarcinoma it is a breakthrough. A treatment that increases the chance of being free from progression by 30% at six months after starting treatment and that prolongs survival from six months with placebo to 10.8 months with ivosidenib, after adjusting for crossover, is definitely meaningful for our patients with cholangiocarcinoma and their families.”

Click here for full prescribing information for Tibsovo.

Click here to learn more about bile duct cancer.
