Opdivo Shows Benefits for Liver Cancer but Falls Short of Survival Target

Immunotherapy led to fewer side effects and better quality of life than standard-of-care therapy.

September 29, 2019 By Liz Highleyman

The checkpoint inhibitor Opdivo (nivolumab) did not reach the statistical threshold for improved overall survival compared with standard targeted therapy for people with advanced liver cancer, but it did appear to be better tolerated, according to research presented at the European Society for Medical Oncology Congress (ESMO 2019) this week in Barcelona.

The median overall survival was 16.4 months for patients taking Opdivo versus 14.7 months for those using Nexavar (sorafenib) in a late-stage study. Although this difference did not meet the study's high bar for statistical significance, meaning it could have been driven by chance, people taking Opdivo had fewer severe side effects and were less likely to stop treatment for this reason.

"The encouraging efficacy and favorable safety profile seen with nivolumab demonstrates the potential benefit of immunotherapy as a first-line treatment for patients with this aggressive cancer," presenter Thomas Yau, MD, of the University of Hong Kong said in an ESMO press release.

Over years or decades, chronic hepatitis B or C, heavy alcohol use and other causes of liver injury can lead to the development of liver cirrhosis and hepatocellular carcinoma (HCC), the most common type of primary liver cancer. HCC is often detected late and is difficult to treat, making it one of the leading causes of cancer death.

Opdivo is a monoclonal antibody that helps the immune system fight cancer. It blocks the PD-1 immune checkpoint receptor on T cells, which plays a role in regulating immune function. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block PD-1 or its binding partner, known as PD-L1, can release the brakes and restore T-cell activity. People with higher PD-L1 levels in their tumors tend to do better on checkpoint inhibitors, but this is not a reliable predictor of individual response.

In 2017, Opdivo was approved for liver cancer patients who had previously tried Nexavar. A previous Phase I/II study (CheckMate-040) showed that Opdivo led to complete or partial tumor shrinkage in about 20% of participants. However, patients who had not previously used Nexavar had a longer median overall survival time than those who had, suggesting Opdivo might be more effective as first-line therapy.

The Phase III CheckMate-459 trial therefore evaluated whether Opdivo would work better than Nexavar for people with advanced HCC who were starting systemic treatment for the first time.

This analysis included 743 adult liver cancer patients with well-preserved liver function (Child-Pugh Class A) and tumors that could not be surgically removed or treated with local therapies. The study did not select participants according to PD-L1 level; about 18% had levels of 1% of higher.

The participants were randomly assigned to receive Opdivo or Nexavar, a kinase inhibitor that interferes with proteins that promote cell growth and blood vessel development. Opdivo was given as an IV infusion every two weeks while Nexavar was taken as a twice-daily pill. Participants continued treatment until they experienced disease progression or unacceptable toxicity.

Those assigned to take Opdivo stayed on the drug for a median of 4.2 months and those assigned to Nexavar did so for 3.7 months. Many people who experienced disease progression on their initial therapy moved on to subsequent medications (38% in the Opdivo group and 46% in the Nexavar group); one in five Nexavar recipients went on to receive immunotherapy.

The findings presented at the ESMO meeting showed that Opdivo did not lead to a statistically significant improvement in overall survival compared with Nexavar. The 12-month overall survival rates were 60% and 55%, respectively, falling to 37% and 33% at 24 months. The median progression-free survival was similar in both groups, at just under four months. However, the data did show a trend toward improved survival and “clinically meaningful” benefit, according to Yau.

The overall response rate, meaning complete or partial tumor shrinkage, was 15% for the Opdivo group compared with 7% for the Nexavar group; 14 Opdivo recipients (4%) and five Nexavar recipients (1%) achieved complete remission. Opdivo recipients with PD-L1 levels of 1% or higher were about twice as likely to respond as those with the lowest levels (28% versus 12%), suggesting this may be used as a biomarker to help select the patients most likely to respond.

Opdivo was generally safe and well tolerated with no new safety concerns or unexpected side effects not seen in earlier studies. Fewer people taking Opdivo experienced severe (Grade 3 or 4) side effects compared with those taking Nexavar (22% versus 49%, respectively), and they were half as likely to stop treatment because of adverse events (4% versus 8%). Skin and gastrointestinal side effects were especially more likely with Nexavar. What’s more, study participants taking Opdivo reported better quality of life, Yau reported.

“[T]hese results are unlikely to change the current standard of care. However, it is becoming more apparent that immunotherapy could have a role for the first-line treatment of advanced HCC and the differences in response rates are clinically meaningful,” commented Angela Lamarca, MD, of the Christie NHS Foundation Trust in Manchester, England. “In a hypothetical scenario in which both options (sorafenib and immunotherapy) were available and reimbursed and if quality of life was shown to be better with nivolumab…clinicians and patients may favor the option with a more tolerable safety profile.”

Experts suggested that Opdivo might have demonstrated a significant survival benefit if the study

had been limited to people with higher PD-L1 levels and if patients had not been able to move on to subsequent therapies.

Opdivo alone and in combination with the CTLA-4 checkpoint blocker Yervoy (ipilimumab) is also being studied as neoadjuvant, or preoperative, therapy for people with liver cancer that can be surgically removed.

Click here for full prescribing information for Opdivo.

Click here to learn more about liver cancer.
