Checkpoint Inhibitors Improve Outcomes for People With Liver Cancer

Treatment with Tecentriq plus Avastin or with Keytruda alone delays disease progression and improves survival.

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Checkpoint inhibitor immunotherapy led to improvements in outcomes for people with advanced liver cancer, according to reports presented last week at the virtual American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI).

Over years or decades, chronic hepatitis B or C, heavy alcohol use, fatty liver disease and other causes can lead to the development of liver cirrhosis and hepatocellular carcinoma (HCC), the most common type of liver cancer. HCC is often detected late and is difficult to treat, making it one of the leading causes of cancer death worldwide. But several new checkpoint inhibitors and targeted therapies have been approved for liver cancer in recent years.

Tecentriq Plus Avastin

Richard Finn, MD, of the Geffen School of Medicine at the University of California, Los Angeles, presented the latest findings from a Phase III study of Tecentriq (atezolizumab) plus Avastin (bevacizumab) for people with inoperable liver cancer, showing that the combination provided the longest overall survival ever seen in a study of first-line treatment.

The international IMbrave150 trial enrolled 501 people with locally advanced or metastatic HCC who had not previously received systemic therapy. They were randomly assigned to receive Tecentriq plus Avastin administered by IV infusion every three weeks or standard treatment with twice-daily oral Nexavar (sorafenib) until they experienced disease progression or unacceptable side effects.

Tecentriq is a PD-L1 checkpoint inhibitor that restores T-cell activity against cancer. Avastin is a monoclonal antibody that blocks VEGF, a protein that promotes the proliferation of blood vessels that supply tumors and plays a role in immune suppression. Nexavar is kinase inhibitor, a type of targeted therapy that blocks enzymes involved in cell growth and blood vessel development.

Primary results presented at a conference in 2019 showed that Tecentriq plus Avastin reduced the risk of death by 42% compared with Nexavar. The overall survival time was 13.2 months in the Nexavar group but was not reached in the Tecentriq plus Avastin group because most patients

were still alive. Overall response rates, meaning complete or partial tumor shrinkage, were 28% with Tecentriq plus Avastin versus 12% with Nexavar.

These findings led to the Food and Drug Administration approval of Tecentriq plus Avastin for HCC in May 2020.

Last week, Finn reported that after additional follow-up, the median overall survival time was 19.2 months with Tecentriq plus Avastin versus 13.4 months with Nexavar—a 34% reduction in the risk of death. The 18-month overall survival rate was 52% with the combination versus 40% with Nexavar. The median progression-free survival (PFS) times were 6.9 months versus 4.3 months, respectively, and the PFS rates were 24% and 12%.

Overall response rates were 30% (including 8% with complete responses) in the Tecentriq plus Avastin group versus 11% (with less than 1% complete responses) in the Nexavar group. Many participants also had stable disease with no further progression, yielding disease control rates of 74% and 55%, respectively.

“We see with longer follow-up that we have more responses” with Tecentriq plus Avastin, including more complete responses, Finn said.

Treatment was generally safe but most participants experienced side effects. Patients who received Tecentriq plus Avastin were more likely to experience fever, abnormal liver and kidney lab tests and infusion reactions, while those taking Nexavar had more diarrhea and hand-foot syndrome (redness, swelling and pain on the palms of the hands and soles of the feet). Overall rates of severe (Grade 3 or 4) adverse events were similar in the two groups (43% versus 46%), but more people taking the combination stopped treatment due to adverse events (22% versus 12%)

Despite the high rate of side effects, people taking Tecentriq plus Avastin reported slower declines in quality of life, physical functioning and role functioning compared with those who took Nexavar, according to a report at last year’s ASCO GI meeting.

“After an additional year of follow-up, these data confirm the superiority of Tecentriq in combination with Avastin compared to sorafenib in patients with advanced HCC,” said ASCO GI program committee member Laura Kulik of the Feinberg School of Medicine at Northwestern University. “These results provide further confidence for physicians and patients in the use of this combination as first-line therapy.”

Click here to read the study abstract.

Keytruda

Updated findings show that Keytruda (pembrolizumab) shrinks tumors in previously untreated people with advanced HCC, and it appears to offer clinical benefits for those who have already used Nexavar.

Like Tecentriq, Keytruda is a checkpoint inhibitor that restores immune activity against cancer, but it blocks the immune-regulating protein PD-1 on T cells rather than its binding partner, PD-L1, on tumor cells.

Keytruda was granted accelerated approval in 2018 based on the results of the Phase II KEYNOTE-224 trial. This nonrandomized study included 104 people with advanced liver cancer who did not respond to or could not tolerate Nexavar. All participants received Keytruda by IV infusion every three weeks.

As previously reported, the overall response rate was 17%, including one complete response. Another 44% had stable disease, for a disease control rate of 61%. The median progression-free survival time was 4.9 months—an improvement over standard therapy. The one-year PFS rate was 28% and the estimated overall survival rate was 54%.

However, the larger Phase III KEYNOTE-240 trial failed to confirm these findings. That study included 413 participants with locally advanced or metastatic HCC who progressed on or could not tolerate Nexavar. They were randomly assigned to receive Keytruda or a saline placebo along with the best supportive care.

Merck announced in 2019 that the study did not meet its primary endpoints of improved overall and progression-free survival. But Keytruda did appear to offer some benefits.

As Finn reported at that year's ASCO annual meeting, the median overall survival was 13.9 months in the Keytruda group versus 10.6 months in the placebo group—a 22% reduction in the risk of death. Although the difference met the traditional threshold for statistical significance, it did not meet the more stringent criteria set for this analysis. The median progression-free survival time was similar in the two groups, 3.0 months and 2.8 months, respectively. Overall response rates were 18% in the Keytruda group versus 4% in the placebo group; six people in the Keytruda group but none in the placebo group experienced complete remission.

Updated results from both studies were presented at the recent ASCO GI meeting.

Jean-Luc Van Laethem, MD, PhD, of Erasmus University Hospital in Brussels, reported findings from a subgroup of 51 participants in KEYNOTE-224 who had not previously used Nexavar.

After nearly two years of follow-up, the overall response rate was 16%, all of which were partial responses. Another 22 patients (41%) had stable disease, yielding a disease control rate of 57%. Those who responded saw a durable benefit: The median duration of response was not reached because most were still responding. An estimated 70% of patients had a response duration of at least a year. The median time to progression was four months and the 12-month PFS rate was 24%. The median overall survival time was 17 months and the 12-month overall survival rate was 58%.

In this study, 14% of participants experienced severe side effects. The most common adverse events were diarrhea, fatigue, hypothyroidism and muscle pain. Three people stopped treatment

due to adverse events and there was one treatment-related death.

Van Laethem said these findings “clearly support further evaluation of pembrolizumab-based regimens in the therapeutic landscape of HCC,” and noted the need to identify biomarkers than could help predict which patients will respond.

Click here to read the study abstract.

Philippe Merle, MD, PhD, of Lyon University hospital Center in France, presented an update from KEYNOTE-240.

After a median follow-up period of more than three years, the median overall survival time was 13.9 months in the Keytruda group compared with 10.6 months in the placebo group. The estimated two-year overall survival rates were 29% versus 20%, respectively. At three years, the corresponding survival rates were 18% and 12%. The median PFS time was 3.3 months versus 2.8 months. The estimated two-year PFS rates were 12% and 5%, respectively, and three-year rates were 9% and 0%. The differences in overall and progress-free survival reached the traditional threshold for statistical significance.

The overall response rates remained the same, at 18% in the Keytruda group and 4% in the placebo group, but the number of people with complete responses rose from six to 10 in the Keytruda group and remained at zero in the placebo group. When stable disease was included, the disease control rates were 62% and 53%, respectively.

Merle noted that the safety profile remained consistent with no new or unexpected side effects, and concluded that these data support a favorable risk-benefit profile for Keytruda.

Click here to read the study abstract.

Click here to learn more about liver cancer.
