Immunotherapy Combo Shows Promise for Advanced Liver Cancer

Opdivo plus Yervoy led to higher response rates and longer survival than Opdivo alone.

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Combining two different types of checkpoint inhibitor immunotherapy led to improved outcomes in people with advanced liver cancer, according to study results presented this week at The Liver Meeting, the annual meeting of the American Association for the Study of Liver Diseases (AASLD).

People treated with the most effective regimen of Opdivo (nivolumab) plus Yervoy (ipilimumab) had an overall response rate of 32% and a median survival of nearly two years—better than the outcomes seen with Opdivo alone. The dual treatment was generally safe and side effects were described as manageable.

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, as it generally does not respond well to traditional chemotherapy. Opdivo and a similar immunotherapy, Keytruda (pembrolizumab), as well as several targeted therapies, have been approved for HCC treatment in recent years.

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. Yervoy is a different type of checkpoint inhibitor that blocks CTLA-4, which turns off immune responses by suppressing T-cell replication.

Bruno Sangro, MD, of Clinica Universidad de Navarra in Spain, presented the latest results from the Phase I/II CheckMate 040 trial, which is evaluating Opdivo alone and in combination with other medications in diverse groups of patients with previously treated advanced liver cancer.

As reported at the 2017 Liver Meeting, this study previously showed that Opdivo alone (known as monotherapy) led to an overall response rate—meaning complete or partial tumor shrinkage—of 14% and a median overall survival of about 16 months for people previously treated with Nexavar (sorafenib), the standard targeted therapy for HCC. In 2017, the Food and Drug Administration

(FDA) granted accelerated approval of Opdivo monotherapy for people with previously treated liver cancer.

The trial subsequently evaluated Opdivo in combination with Yervoy. This analysis included 148 people with advanced HCC who had previously taken or could not tolerate Nexavar. About 80% were men, two thirds were Asian and the median age was 60 years.

In most cases, the cancer had spread beyond the liver. About half had hepatitis B, 22% had hepatitis C and 22% had neither virus. About one in five had PD-L1 levels of 1% or higher, a factor that has been found to predict better response to Opdivo in some studies.

Study participants were randomly assigned to receive one of three different dosing regimens of Opdivo plus Yervoy, continuing treatment until they experienced disease progression or unacceptable side effects:

- Arm A: 1 milligram per kilogram Opdivo + 3 mg/kg Yervoy every three weeks for four cycles, followed by 240 mgOpdivo every two weeks
- Arm B: 3 mg/kg Opdivo + 1 mg/kg Yervoy every three weeks for four cycles, followed by 240 mg Opdivo every two weeks
- Arm C: 3 mg/kg Opdivo every two weeks + 1 mg/kg Yervoy every six weeks

Researchers presented the first combination therapy data at this year's American Society of Clinical Oncology annual meeting in June. Sangro provided further details at The Liver Meeting.

The regimen used in Arm A proved to be most effective. Although overall response rates were similar in Arms A, B and C (32%, 31% and 31%, respectively), the complete response rate, meaning full tumor regression, was highest in Arm A, at 8%.

However, the median overall survival was about twice as long in Arm A (22.8 months) compared with Arms B (12.5 months) and C (12.7 months). At 12 months, the overall survival rates were 61%, 56% and 51% in the three arms. At 24 months, the corresponding rates were 48%, 30% and 42%.

Looking only at the most effective regimen used in Arm A, the overall response rates were similar for were people with hepatitis B (32%), hepatitis C (29%) or neither virus (31%). But the median overall survival was substantially longer for those with hepatitis B (22.2 months) or neither virus (22.8 months) compared with hepatitis C (14.9 months).

Responses occurred across PD-L1 expression levels. Overall response rates in Arms A and B were around 30% regardless of whether patients had PD-L1 levels above or below 1%. In Arm C, however, the response rate rose to 50% for those with PD-L1 levels of 1% or higher.

The combination was generally safe, but severe (Grade 3 or 4) side effects were common: 53% in

Arm A compared with about 30% in Arms B and C. However, most treatment-related adverse events were manageable and reversible, according to Sangro.

Checkpoint inhibitors work by restoring immune responses against cancer cells, but they can also activate the immune system more broadly. Immune-mediated adverse events were more frequent in Arm A, probably an indication that the treatment was more potent in this group. Liver inflammation was the most common severe immune-mediated side effect (20% in Arm A), followed by skin rash, endocrine problems, lung inflammation and colon inflammation (all 6% or less). Most of these individuals were treated with a short course of corticosteroids.

On the day of the presentation, Bristol-Myers Squibb—which makes both Opdivo and Yervoy—announced that the FDA had accepted its supplemental request for approval of the combination for previously treated advanced liver cancer and granted it a breakthrough therapy designation, intended to speed up the development and review of therapies for serious conditions without good existing treatment options.

Sangro noted that a new Phase III clinical trial, CheckMate 9DW, was recently started to evaluate the Opdivo plus Yervoy combination versus the targeted therapies Nexavar or Lenvima (lenvatinib) as first-line treatment for advanced HCC.

As reported at the European Society for Medical Oncology Congress in September, the CheckMate-459 trial found that Opdivo monotherapy did not reach the statistical threshold for improved overall survival compared with Nexavar, though it did double the overall response rate and appeared to be better tolerated. The new study aims to determine whether adding Yervoy can improve response rates and prolong survival without causing unacceptable side effects.

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