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Immunotherapy-Based Approaches for First-Line Treatment of Advanced HCC: The Evidence

Announcer:
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Dr. Venook:
Hello and welcome to CME on ReachMD. I'm Dr. Alan Venook, and today I'll review the current guidelines for immunotherapy-based approaches in the first-line treatment of advanced hepatocellular carcinoma.

Hepatocellular carcinoma is now a very active area of research and the changes in the treatment paradigm are really remarkable over the last decade or so. First things first, everything we talk about today in terms of advances will be restricted to a small population of patients with hepatocellular carcinoma. Those are patients who have well-preserved liver function. And a reminder of what that is and how that's scored is the so-called Child-Pugh score of liver cirrhosis, which rates patients based on their intact or not-intact liver function, since liver dysfunction or liver disease with cirrhosis is very often associated with hepatocellular carcinoma. So that's an important factor. Everything I talk about will be for the patients who have preserved liver function based on Child-Pugh score, which really is a score that was created many decades ago and is still used by FDA as well as providers these days when making this decision.

So in this population of patients with preserved liver function, we first discovered that there was an active drug. Not until 2007 did we have any evidence that there was a therapy that worked in patients with hepatocellular carcinoma. And that first therapy to show of efficacy was sorafenib. That's a tyrosine kinase inhibitor that showed benefit both in patients in a study in Asia-Pacific region as well as what's called the SHARP trial which was in Europe and the US.

Sorafenib was compared to placebo and conferred a survival benefit in both those studies that was similar. The patients in Asia-Pacific did not live as long across the board as patients in the US and Europe, but that changed the entire way we looked at HCC, knowing now that there was an active drug for patients with HCC. So sorafenib became the standard.

Now, if we look at the hepatocellular guidelines within the NCCN Guideline panel in 2008, this slide shows you not a very complex algorithm. Patients who had advanced disease could be offered a clinical trial or sorafenib or supportive care. Really, not much to choose from, but that was the standard in 2008.

Fast-forward to today. I should say we didn't really fast-forward; we slow-forwarded. And that is over the next decade, we had many studies enumerated here on this slide that failed to show a benefit to any drugs compared to sorafenib. It was thought to be low-hanging fruit, but it was not.

If you look at today's guidelines now, you'll see it's a complex page of many treatment options with preferred regimens, with other recommended regimens that are not preferred, and other regimens still, as well as many under study. And I'll talk to you about each of those. The majority of these combine one therapy or another with immunotherapy. So let's go forward to that.

The definitive study that changed the landscape for HCC was called the IMbrave study. That was published in *The New England Journal*

in 2020, and this study looked at patients receiving atezolizumab with bevacizumab – atezolizumab is a checkpoint inhibitor; bevacizumab, of course, is an anti-VEGF drug – versus sorafenib. And the combination of these two drugs versus sorafenib in very select patients, patients who had had upper endoscopy and excluded the presence of varices, again, in this very elite Child's-Pugh category of preserved liver function. And this study, IMbrave150, established atezolizumab/bevacizumab as a standard. This was in 2020. And it remains a standard today for patients with preserved liver function without varices.

Now, going beyond that has been a challenge. In some ways, it was a matter of what the control arm was. And many studies initiated back in that era still used sorafenib as a control arm, even though we had something superior to sorafenib in the atezo/bev study. And I think the next relevant study to talk about the other drugs that are approved in this setting is the so-called STRIDE study. This is a study that looked at the combination of durvalumab/tremelimumab versus sorafenib. So sorafenib served as a control arm in this study because it was launched before the IMbrave results were done.

Tremelimumab is an anti-CTLA4 antibody and durvalumab is a checkpoint inhibitor. The combination versus sorafenib. So two immunotherapies at different mechanisms versus sorafenib demonstrated the superiority of the combination, so-called STRIDE combination, versus sorafenib. So that is also a preferred treatment. The patient population was a little less than IMbrave, but still, the patients with preserved liver function and Child-Pugh score 1, those are the two main options, at least first-line options, that we prefer.

Since then, there have been other studies that have also demonstrated efficacy of other agents in immune therapy range. One of them is a study looking at tislelizumab versus sorafenib. That was published in *JAMA Oncology* in 2023, and that drug was also approved recently by the FDA and is also on the guidelines list, again, compared to sorafenib. All of these studies initiating before the IMbrave was approved. And also commenting, making sure you realize, none of these winning arms have been compared one to the other. So durvalumab versus tezo/bev versus tislelizumab have not and are unlikely to be compared one to the other.

And then I think, also, the advances are not restricted to HCC. We'll also hit on, for a moment, on biliary cancers, which we now know have multiple targets, some immune and some not immune. This slide shows you the molecular targets that have borne fruit in biliary cancer and the impact we've had with a variety of studies. And as you see in this study, KEYNOTE-966, this is patients who received pembrolizumab, the checkpoint inhibitor, with gemcitabine and cisplatin, the chemotherapy combination favored for advanced biliary tract cancers, versus the chemotherapy alone, gemcitabine and cisplatin. And this study, again, demonstrated superiority to pembrolizumab in this population and has led to its approval as a first-line preference for patients with biliary tract cancers.

So here you have, really, over the course of a few years, we've changed the face of hepatobiliary cancers, hepatocellular carcinoma, and biliary tract cancers. A lot to choose from and more work going on now to try to even improve on these further.

Thank you for your attention.

Announcer:
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