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VIEWPOINT

Drug Approvals in Hepatocellular Carcinoma—Filling the Nonexistent Gap?

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Hepatocellular carcinoma (HCC) is an aggressive cancer that mostly affects patients with chronic liver disease and cirrhosis. Hepatocellular carcinoma is usually diagnosed late in its course; hence, the disease has a median survival of only 6 to 20 months.[1] In addition to numerous surgical and interventional therapies, systemic molecularly targeted therapies and immune checkpoint inhibition form an important backbone in the treatment of HCC. Recently, the US Food and Drug Administration (FDA) approved the combination of nivolumab and ipilimumab for use in patients with HCC previously treated with sorafenib tosylate.[2] In this Viewpoint, we critically appraise the evidence behind FDA drug approvals for HCC.

Survival in HCC has always depended on both the degree of hepatic dysfunction as well as tumor biology. Traditionally, HCC was considered a chemotherapy-refractory tumor owing to the high rates of drug resistance, although agents such as doxorubicin were attempted. Yet no FDA-approved therapy existed for patients with advanced-stage HCC until the approval of sorafenib on November 19, 2007.[3] The approval was based on the multicenter, phase 3, double-blind, placebo-controlled Study of Heart and Renal Protection (SHARP) trial. SHARP randomly assigned 602 patients with advanced HCC, predominantly with favorable Childs-Pugh disease and without previous systemic treatment, to receive either sorafenib tosylate (at a dose of 400 mg twice daily) or placebo.[4] The primary outcome of overall survival (OS) was met with median OS benefit in the sorafenib group (10.7 vs 7.9 months; hazard ratio [HR], 0.69; 95% CI, 0.55-0.87; $P < .001$).[4]

For the next decade (**Figure**), no new systemic therapies were approved for HCC until the approval of regorafenib in second-line settings on April 27, 2017. The Regorafenib for Patients With Hepatocellular Carcinoma Who Progressed on Sorafenib Treatment (RESORCE) trial[5] was a randomized, double-blind, parallel-group, phase 3 trial that enrolled adults with HCC whose disease progressed while using sorafenib and was restricted to those with Child-Pugh class A liver function. The trial demonstrated OS benefit with regorafenib over placebo (10.6 vs 7.8 months, HR, 0.63; 95% CI, 0.50-0.79; $P < .001$), which subsequently led to the drug's approval.

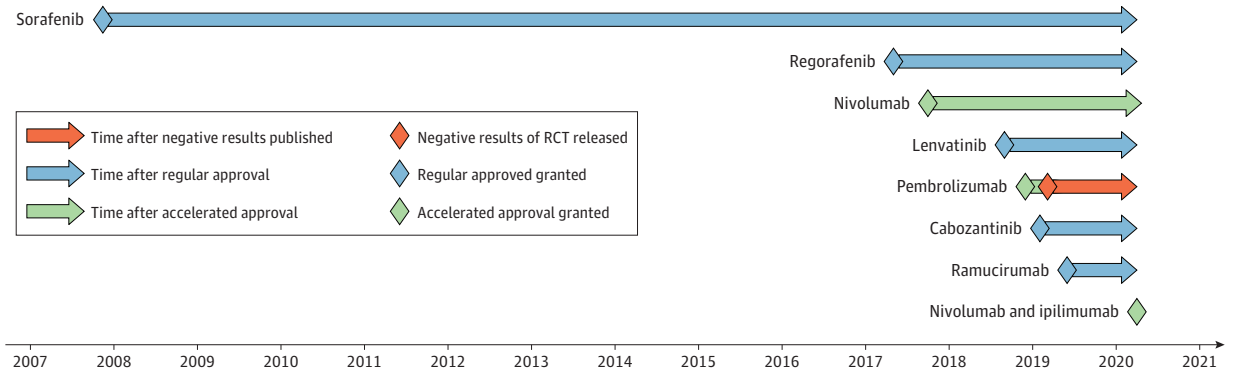
Over the past 3 years, 6 drugs have been approved for HCC, including lenvatinib mesylate in the first-line setting as well as nivolumab, pembrolizumab, cabozantinib s-malate, ramucirumab, and, most recently, a combination of nivolumab and ipilimumab in the second-line setting. (Atezolizumab and bevacizumab was approved after the writing of this article.) Various concerns have been raised regarding these drug approvals and the magnitude of clinical benefit provided.

First, the approval of lenvatinib was based on noninferiority in OS compared with sorafenib in patients with unresectable HCC (13.6 vs 12.3 months; HR, 0.92; 95% CI, 0.79-1.06). Notably, in the trial the upper bound for the noninferiority margin was HR 1.08, and the trial used unequal dose reductions, which occurred in 37% of patients.[6] Specifically, the dose reduction for patients taking sorafenib decreased from 100% of the starting dose to 50% to 25%, whereas the dose reduction for patients taking lenvatinib decreased from 100% to 67% to 33%. Drawing firm conclusions about the effectiveness of drugs is difficult in settings where dose reductions are common and unequal in size. Drugs with smaller-sized dose reduction steps are given an advantage in such a situation; in this case, use of sorafenib would be penalized, as patients experience a larger pharmacologic reduction in this anticancer drug at the same level of adverse events. This principle was described in detail in prior work.[7]

Second, most second-line agents were approved either in a single-arm trial, based on surrogate end points such as the overall response rate (ORR), or against a weak comparison group (eg, placebo). Accelerated approvals were given to 3 of the 6 drugs for use in the second-line setting. For HCC, the overall response rate has been used as a surrogate end point for accelerated approvals of nivolumab, pembrolizumab, and, more recently, nivolumab plus ipilimumab. However, the overall response rate has not been validated as a surrogate end point for HCC. That is, there is no surrogate validation study that has established the response rate as a suitable surrogate for overall survival in this disease. Moreover, results of confirmatory trials have been negative. Specifically, as shown in the Figure, 1 randomized clinical trial of pembrolizumab failed to meet the co-primary end points of OS and progression-free survival. The use of a nonvalidated surrogate end point, as well as negative results on postmarketing studies, suggests that the approval of these agents may not improve patient-centered outcomes.

Third, the use of accelerated approval also requires a treatment indication to be deemed an "unmet medical need." Arguably, before the approvals of regorafenib, cabozantinib, and ramucirumab—all justified based on randomized trials indicating survival benefit—their use as second-line agents for HCC was an unmet need. As shown in the Figure, the FDA used the accelerated approval pathway both before and after these 3 regular approvals. Because accelerated approval is predicated on the fact that an indication is an unmet need, it seems difficult to make this case when drugs with

Figure. Timeline of Drug Approvals by the US Food and Drug Administration for Hepatocellular Carcinoma as of March 2020



Sorafenib was given as sorafenib tosylate; lenvatinib, as lenvatinib mesylate; and cabozantinib, as cabozantinib s-malate. RCT indicates randomized clinical trial.

demonstrated survival benefit have already been approved for this indication, as with HCC.

Fourth, the approval of regorafenib raises concerns over both the marginal clinical benefit in a trial setting and drug toxicity. More important, the structural similarity between regorafenib and sorafenib—a difference of a single-fluorine molecule—raises the question whether the drug actually brings any benefit. Particularly, had regorafenib been tested against sorafenib? Notably, before this study, experts had advocated for the use of sorafenib after disease progression among patients who had tolerated first-line treatment with the drug, given its continued antitumor effect.[8]

Fifth, most randomized controlled trials that used clinically significant end points such as OS had a weak comparison group in the placebo arm. None of these approved drugs was studied head to head except sorafenib and lenvatinib in a noninferiority trial.[6] This begs the relevant clinical question the clinical trials are designed to answer: Which second-line drug is best, or would it be better to continue the use of sorafenib in the select patients able to tolerate second-line therapy?

Finally, the overarching question across all drug approvals in this space is this: Are we making progress? The history of FDA approvals in HCC has demonstrated approval of drugs with no uncertain benefit over the current standard of care when drugs with actual OS benefit in first- and second-line treatment already exist. Does this regulatory program maximize patients' best interests or merely provide options of uncertain gain?

ARTICLE INFORMATION

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