Association between sustained virological response and clinical outcomes in patients with hepatitis C infection and hepatocellular carcinoma

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BACKGROUND: Sustained viral response (SVR) improves survival for patients with hepatitis C (HCV) and hepatocellular carcinoma (HCC) after curative treatment; however, the benefit of SVR in those with active HCC with a significant competing risk of mortality is unknown. This study aimed to evaluate the association between SVR and outcomes in patients with active HCC.

METHODS: The authors performed a multicenter, retrospective cohort study including consecutive adults with HCV cirrhosis and treatment-naïve HCC diagnosed between 2014 and 2018. Patients were stratified into two groups: active viremia (n = 431) and SVR before HCC diagnosis (n = 135). All patients underwent nonsurgical therapy as their initial treatment and were followed until liver transplantation, last follow-up, or death. The primary outcome was incident or worsening hepatic decompensation within 6 months and the secondary outcome was overall survival. All analyses used inverse probability of treatment weights (IPTW) to account for differences between the nonrandomized cohorts.

RESULTS: Post-SVR patients had significantly lower odds of hepatic decompensation compared to viremic patients (odds ratio [OR], 0.18; 95% confidence interval [CI], 0.06–0.59). Results were consistent among subgroups of patients with Child Pugh A cirrhosis (OR, 0.22; 95% CI, 0.04–0.77), Barcelona Clinic Liver Cancer stage B/C HCC (OR, 0.20; 95% CI, 0.04–0.65), and those receiving nonablative HCC therapies (OR, 0.21; 95% CI, 0.07–0.67). However, in IPTW multivariable Cox regression, SVR was not associated with improved survival (hazard ratio, 0.79; 95% CI, 0.56–1.12).

CONCLUSIONS: Patients with HCV-related HCC and SVR are less likely to experience hepatic decompensation than viremic patients, suggesting patients with HCC who are undergoing nonsurgical therapies may benefit from DAA treatment.

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KEYWORDS: DAA, decompensation, HCC, HCV, SVR.

INTRODUCTION

Chronic hepatitis C (HCV) remains a leading cause of chronic liver disease and hepatocellular carcinoma (HCC) worldwide for nearly 20,000 deaths annually in the United States. Chronic HCV infection leads to progressive fibrosis that can result in cirrhosis and its associated complications. Despite recommendations for universal screening for HCV and availability of highly effective direct acting antivirals (DAAs) for the treatment of HCV, there remains a reservoir of patients with untreated HCV who present with cirrhosis and HCC.

Treatment of HCV forstalls fibrosis progression, decreases HCC risk, and can improve patient reported outcomes in patients with cirrhosis. DAA therapy has been shown to be highly efficacious with near universal cure rates, even in patients with cirrhosis. The review and approved or exempted by each institutional review board (IRB), and data use agreements were used to share de-identified data: "University of Michigan IRB, HUM00083743; University of Chicago IRB, IRB19-1026; Cedars Sinai IRB, CSR17682; University of Texas Southwestern IRB, 201911-0014; University of California San Francisco IRB, CA-0157549; University of North Carolina IRB, IRB Exempt; Henry Ford IRB, IRB Exempt; University of Pennsylvania IRB, IRB Exempt; and Virginia Commonwealth, IRB Exempt.

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in patients with a history of HCC.7,8 We have previously shown DAA therapy after complete HCC response is not associated with increased risk of HCC recurrence and is in fact associated with improved overall survival, mediated through sustained virological response (SVR).9,10

However, the benefits of DAA therapy in patients with active HCC remain unclear, and practice patterns regarding treatment vary widely.11,12 Prior analyses estimating the benefit of HCV therapy in active HCC have focused on early-stage patients undergoing surgical therapy, with few data in patients with intermediate- or advanced-stage disease.13 These more advanced-stage patients have a substantial competing risk of mortality from HCC, and whether treatment of the HCV is indicated is unclear. Furthermore, with approval of more efficacious systemic therapies for advanced-stage HCC, the question of whether patients benefit from HCV treatment at the time of HCC diagnosis is increasingly salient, particularly in patients with a high competing risk of mortality from HCC.14 Furthermore, deterioration in liver function is a major cause of lack of eligibility for treatment with systemic or locoregional HCC therapies.15 We aimed to compare the association between SVR and hepatic decompensation and overall survival in patients with HCC undergoing nonsurgical therapies.

MATERIALS AND METHODS

Design

We performed a multicenter retrospective cohort study at nine US centers from the North American Liver Cancer (NALC) Consortium, including consecutive patients with HCV-related HCC from January 2014 to June 2018. We included adult (18+ years old) patients with a documented history of HCV RNA positivity who had treatment-naive HCC diagnosis per the American Association for the Study of Liver Diseases guidelines (i.e., histologic confirmation or lesions >1 cm with characteristic appearance on imaging [arterial enhancement and delayed washout]). Because most patients who receive surgical HCC therapy are treated for HCV after surgery, we only included patients whose first HCC treatment was nonsurgical in nature: local ablation, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), or systemic therapy. We also excluded patients who were lost to follow-up within 3 months of HCC diagnosis, those that lacked complete laboratory components of the Child-Turcotte-Pugh (CTP) score within 12 months of diagnosis, or those with a history of other active malignancy during study period (except for nonmela-
noma skin cancer) (Fig. S1). We excluded patients with SVR from interferon-based therapies. The cohort was split into two groups: (1) those with active HCV viremia at the time of HCC diagnosis, and (2) those who had achieved SVR before HCC diagnosis. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies were used for this study (Supporting information).16 Institutional review board approval was obtained at all sites involved in this study and de-identified data were transferred to the University of Michigan through data use agreements.

Outcomes

Our primary outcome was new or worsening hepatic decompensation within 6 months of HCC diagnosis. We defined new hepatic decompensation as new onset ascites requiring diuretics or paracentesis, new onset hepatic encephalopathy (HE) requiring lactulose and/or rifaximin, new onset variceal bleeding documented on upper endoscopy, or increase in Child Pugh score ≥2 points from time of HCC diagnosis. We defined worsening decompensation as ascites newly requiring paracentesis, hepatic encephalopathy requiring hospitalization despite lactulose compliance, addition of rifaximin to an existing regimen of lactulose, or increase in Child Pugh score ≥2 points. We performed sensitivity analyses with different time points for development of decompensation (3 and 9 months). Patients were censored at the time of death or liver transplantation. Our secondary outcome was overall survival measured from time of HCC diagnosis (defined as time 0). Patients with active viremia at time of HCC diagnosis were censored at initiation of DAA therapy that led to SVR.

Data collection

We used a standardized data collection template to obtain demographic and clinical variables at HCC presentation from electronic medical records at each site, including age, sex, race, ethnicity, platelet count, aspartate aminotransferase, alanine aminotransferase, HCV viral load, HCV genotype, Eastern Cooperative Oncology Group performance status, and α-fetoprotein (AFP). In HCV-treated patients, we collected DAA regimen and time from HCC diagnosis to DAA initiation. Degree of liver dysfunction was assessed by Child-Pugh and Model for End-Stage Liver Disease scores and presence and severity of hepatic decompensation. Tumor burden, as determined by interpretation of imaging by local radiologists at each site, was categorized according
to Barcelona Liver Cancer Classification (BCLC) staging. We recorded the number and type of HCC treatments with subsequent tumor response. We recorded liver function and presence of hepatic decompensation at 3, 6, 9, and 12 months after HCC diagnosis. Data was collected until death, last follow-up, or liver transplantation.

Analytic plan
To account for the nonrandomized nature of the data, we performed inverse probability of treatment weighted (IPTW) analyses when comparing outcomes between groups. Patient-level weights were calculated as the inverse of the probability of receiving the observed treatment. The probability (propensity) of treatment was estimated from logistic regression models including all variables thought to possibly be associated with treatment assignment and/or outcome. Two such models were developed; one using all relevant covariates and the other excluding variables related to liver function. We performed the latter model given DAA therapy could influence liver function, and adjusting for liver function at time of HCC treatment may capture some of DAA treatment effect on post-HCC outcomes. Hepatic decompensation was summarized as binomial proportions and compared between groups using logistic regression models also adjusting for other covariates and both using IPTWs. We also included a subject-level random intercept to account for possible between-patient, within-center, correlation. Our primary interest was centered on comparing outcomes between the viremic and SVR HCC cohorts; we also performed a post hoc subgroup analysis comparing outcomes between DAA-exposed and DAA-naïve viremic patients. A key secondary end point was overall survival (OS) calculated as the time from HCC treatment to death from any cause with censoring at the earliest of last follow-up or liver transplantation. OS was compared between the cohorts using log-rank tests and score tests in Cox models with center-level frailty (random effect) and other potential confounding variables. All analyses were conducted using SAS software, Version 9 (SAS).

RESULTS

Patient characteristics
In total, there were 135 patients in the SVR-HCC group and 431 patients in the viremic-HCC group with their baseline characteristics shown in Table 1. Compared to the viremic-HCC group, patients in the SVR-HCC group were older, had a higher proportion of females, and higher proportion of non-Hispanic White patients. Patients in the SVR-HCC group also had earlier stage disease, with a higher proportion having BCLC stage 0/A (59.6% vs. 45.7%), smaller median maximum tumor diameter (2.6 vs. 3.2), and less vascular invasion (11.0% vs. 18.3%) or extrahepatic disease (5.9% vs. 10.2%). Hepatic decompensation at baseline was present in approximately one-third of the cohort, with the viremic-HCC group having a higher prevalence of ascites (33.9% vs. 27.4%) and the SVR-HCC group having a higher prevalence of hepatic encephalopathy (24.4% vs. 19.9%). The viremic-HCC group and SVR-HCC groups had similar median MELD scores (10 vs. 9). The characteristics of the cohorts after IPTW weighting are shown in Table 1, which showed balanced cohorts without significant differences between the groups.

For patients in the SVR-HCC group, the median time from initiation of DAA therapy to HCC diagnosis was 17.7 months (interquartile range [IQR], 8–28). For the viremic cohort, 27.3% of patients were treated with DAs on follow-up, a median of 14.5 months (IQR, 9.5–19) from HCC diagnosis. The median follow-up time after HCC diagnosis of the entire cohort was 29 months (27 months in the SVR-HCC and 30 months in the viremic-HCC group). Median time from HCC diagnosis to the first cancer treatment was 55 days (IQR, 42–81) in the SVR-HCC group versus 58 days (IQR, 36–94) in the viremic-HCC group ($p = .58$). The most common initial therapies were TACE (51.2%) followed by ablation (13.1%) and systemic therapy (9.0%). The median number of total therapies received was two (IQR, 1–3) in the SVR-HCC group versus two (IQR, 1–3) in the viremic-HCC group. At the end of the observed follow-up, 42% of patients had died (45% in viremic-HCC vs. 31% in SVR-HCC) and 11% had undergone liver transplantation (13% in viremic-HCC vs. 6% in SVR-HCC).

Hepatic decompensation
In IPTW analysis, patients with SVR-HCC had significantly less hepatic decompensation than patients with viremic-HCC, with the incidence of new or worsening hepatic decompensation detailed in Figure 1 (log-rank $p < .001$). Kaplan–Meier estimates of the proportion of patients with clinical decompensation or an increase in CTP score ≥2 within 6 months after HCC diagnosis are 7% of the SVR-HCC group and 23% of the viremic-HCC group. The most common new or worsening decompensation was ascites (9%), followed by HE (4%).
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and variceal bleeding (1%), with no difference in pattern of hepatic decompensation between the two groups. In IPTW logistic regression analysis examining decompensation at a fixed time point of 6 months from diagnosis, adjusted for baseline CP and first HCC treatment as covariates, SVR-HCC patients had a lower adjusted risk of decompensation compared to viremic-HCC patients (OR, 0.18; 95% CI, 0.06–0.59). Results were similar in a subgroup analysis excluding patients who underwent local ablation as initial therapy (OR, 0.21; 95% CI, 0.07–0.57). In sensitivity analyses, a lower risk of hepatic decompensation continued to be observed in the SVR-HCC group at 3 months (OR, 0.41; 95% CI, 0.19–0.82) and 9 months (OR, 0.46; 95% CI, 0.20–0.93).

Overall survival
Median survival from HCC diagnosis for the SVR-HCC group was 49 (95% CI, 26, not reached) months whereas the viremic-HCC group had a median survival of 34 months (95% CI, 29–40). The IPTW Kaplan–Meier estimates of survival from diagnosis were similar between the two cohorts (hazard ratio [HR], 0.75; 95% CI, 0.53–1.07; log-rank test p = .21) (Fig. 2). In the IPTW Cox multivariable model, OS was not significantly different in the viremic and SVR-HCC group; (adjusted HR, 0.79; 95% CI, 0.56–1.12). Results were similar in a sensitivity analysis excluding patients who underwent local ablation as initial therapy (HR, 0.77; 95% CI, 0.52–1.14).

TABLE 1. Baseline characteristics of patients at the time of HCC diagnosis before and after IPTW

| Baseline cohort | Post SVR HCC (n = 135) |
|-----------------|------------------------|
| Viremic HCC (n = 431) | Post SVR HCC |
| Age (mean±SD), y | 60.9±6.3 | 64.1±6.4 |
| Male sex % (n) | 81.6 (510) | 75.4 (141) |
| Race % (n) | | |
| White | 57 (245) | 62 (117) |
| Black | 26 (114) | 25 (54) |
| Asian | 2 (11) | 3 (6) |
| Other | 9 (40) | 4 (5) |
| Unknown | 5 (22) | 6 (8) |
| Ethnicity % Hispanic (n) | 14.4 (90) | 10.6 (20) |
| BCLC class % (n) | | |
| 0/A | 42.9 (268) | 57.2 (107) |
| B | 26.7 (167) | 19.2 (36) |
| C/D | 27.0 (169) | 19.7 (37) |
| Tumor no. % (n) | | |
| 1 | 58.5 (364) | 72.4 (136) |
| 2 | 24.9 (155) | 19.7 (37) |
| 3+ | 16.5 (103) | 8.0 (15) |
| Diameter of largest tumor, median (IQR) | 3.2 (2.9, 3.5) | 2.6 (2.2, 3.0) |
| Vascular invasion % | | |
| 18.3 (79) | 11.1 (15) |
| Distant metastases % | | |
| 14.2 (61) | 8.9 (12) |
| ECOG, median (IQR) | 0 (0,1) | 0 (0,1) |
| Child Pugh % A/B/C | 55/38/7 | 67/27/6 |
| MELD, median | 10 | 9 |
| Median AFP (IQR) | 28 (5, 3190) | 9 (3, 1230) |
| Median platelet count (IQR) | 103 (51, 256) | 107 (49, 218) |
| Hepatic encephalopathy % (n) | 20.2 (126) | 29.4 (55) |
| Ascites % (n) | 37.0 (231) | 31.0 (58) |
| No. of HCC therapies (IQR) | 2 (1, 3) | 2 (1, 3) |
| Initial HCC therapy % (n) | | |
| TACE | 52.9 (228) | 45.9 (62) |
| Ablation | 10.7 (48) | 20.7 (28) |
| TARE | 9.3 (41) | 8.8 (12) |
| Systemic | 9.3 (40) | 8.9 (12) |
| SBRT | 8.3 (36) | 8.1 (11) |
| Other | 9.3 (40) | 7.4 (10) |

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Cancer Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weights; IQR, interquartile range; MELD, Model For End-Stage Liver Disease; SBRT, stereotactic body radiation therapy; SVR, sustained virological response; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.
Subgroup analyses
Patient with Child-Turcotte-Pugh class A cirrhosis
Figure 3A,B shows the comparison of decompensation and overall survival between the viremic-HCC and SVR-HCC groups among patients with CTP A cirrhosis at baseline. Similar to the primary analyses, IPTW analysis demonstrated lower odds of decompensation at 6 months (OR, 0.26; 95% CI, 0.06–0.78) and nonsignificant improvement in OS (HR, 0.61; 95% CI, 0.37–1.02) in the SVR-HCC group compared to the viremic-HCC group.
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Figure 3A,B compares the incidence of hepatic decompen- sation and overall survival between the viremic- HCC and SVR- HCC groups among those with BCLC stage B or C HCC. IPTW analysis showed lower odds of decompensation at 6 months in the SVR- HCC group (OR, 0.20; 95% CI, 0.04–0.65) as well as non- significant improvement in OS (OR, 0.72; 95% CI, 0.46–1.14).

Patients with BCLC stage B/C HCC

Figure 3A,B compares the incidence of hepatic decompen- sation and overall survival between the viremic- HCC and SVR- HCC groups among those with BCLC stage B or C HCC. IPTW analysis showed lower odds of decompensation at 6 months in the SVR- HCC group (OR, 0.20; 95% CI, 0.04–0.65) as well as non- significant improvement in OS (OR, 0.72; 95% CI, 0.46–1.14).

Viremic patients with prior exposure to DAAs

A post hoc subgroup analysis comparing DAA-exposed (n = 20) to DAA-naive (n = 411) viremic patients demonstrated similar OS between the two groups (log-rank p = .61). Kaplan–Meier estimates for 2-year OS were 64% and 69% in patients treated and not treated with DAAs before HCC diagnosis, respectively. The proportion of patients experiencing decompensation was 5% versus 19% at 6 months (p = .13) and 24% versus 19%
at 9 months ($p = .63$) for patients treated and not treated with DAAs before HCC, respectively.

DISCUSSION

Treatment of HCV has been associated with benefits across the spectrum of fibrosis stage and in patients with a history of HCC after curative treatment. In this analysis, using a nationally representative multicenter cohort, we showed SVR is associated with decreased risk of hepatic decompensation in patients with HCV-related HCC receiving noncurative therapies. This finding was consistent in key subgroups of patients with CTP A cirrhosis and with intermediate or advanced (BCLC B/C) stage HCC—patients with the highest competing risk of HCC-related mortality. SVR was also associated with improved survival, although the difference did not reach statistical significance.

Our work builds on the growing body of evidence showing the benefit of SVR in patients with cirrhosis by preventing disease progression and reducing hepatic decompensation. Liver disease progression is known to be a major driver of prognosis in compensated patients with early-stage HCC, and our group has demonstrated the safety and benefit of DAA therapy in patients who have undergone curative treatment. In this study, we similarly find patients with HCC who previously achieved SVR have significantly reduced risk of hepatic decompensation compared to those who remained viremic at time of HCC diagnosis. However, the reduced risk of hepatic decompensation did not translate into improved overall survival, likely due to the substantial competing risk of HCC mortality in this cohort. Although the study was conducted after the availability of systemic therapies for HCC, the study period preceded availability of currently available second-line therapies as well as immune checkpoint inhibitors including atezolizumab-bevacizumab—that have significantly improved prognosis for patients undergoing noncurative therapies. As median survival for patients with BCLC B and C disease extends from 1 to 2 years to 2–3 years, preservation of liver function will likely become increasingly beneficial. Preservation of liver function may also be critical to allow sequential therapies, including second- and potentially even third-line systemic therapy options in some patients. Although further data are needed in HCC patients undergoing treatment in this contemporary therapeutic landscape, our study suggests patients with HCC may benefit from DAA treatment in the interim. Only 27.3% of patients in the viremic cohort were treated with DAA therapy on follow-up, highlighting the wide variance in practice in treatment of HCV.

Decisions regarding the benefit of HCV treatment in patients with active HCC would not only need to consider potential OS benefits of SVR but also other factors such as impact on quality of life, likelihood of SVR, and costs. Although several studies have demonstrated that patients with HCV who achieve SVR, including those with cirrhosis, have improved quality of life, it is unknown if this benefit would be observed in patients with HCC who can have other drivers for impaired quality of life. Second, in this study, we compared patients with post-SVR de novo HCC to those with active viremia at HCC diagnosis; however, several studies have demonstrated patients with active HCC have reduced SVR rates compared to non-HCC patients. Therefore, our study mirrored a per-protocol analysis of HCV treatment benefit, rather than intention-to-treat analysis. Finally, DAA therapy has been shown to be cost-effective in patients with HCV but HCC-specific studies should be performed, considering the above factors.

Our study has many strengths and weaknesses that warrant further attention. The data collected were retrospective, allowing for ascertainment bias in key outcome variables such as hepatic decompensation or overall survival. All included sites are tertiary referral centers with high levels of patient retention and ability to collect data from connected referral facilities, which minimizes the risk of this bias. Unmeasured confounding is a well-described limitation of retrospective analyses; however, we were able to reliably collect data on all known mediators of hepatic decompensation and overall survival for the purposes of this analysis, minimizing this risk. Third, SVR occurred before diagnosis of HCC, so the estimated benefits of HCV treatment and/or achieving SVR in patients with active HCC may be overestimated. Finally, there were inherent group differences in baseline characteristics between viremic-HCC and SVR-HCC patients; however, we attempted to balance known and measurable confounders through IPTW analyses. All known mediators of decompensation were equally balanced between the groups in the IPTW analyses, although there is still potential for selection bias and unmeasured confounders that may have impacted our results. These limitations were judged to be outweighed by the study’s notable strengths, including its multicenter design with a large cohort of patients, rigorous statistical analysis plan and
consistent results across key subgroups. These data are likely the most robust evidence for the benefits of SVR in this population outside of a prospective randomized trial for DAA treatment in this population.

In conclusion, we have shown the benefits associated with SVR in patients undergoing noncurative therapies for HCV in a large multicenter analysis. Although the impact on subsequent hepatic decompensation were most profound, there was also numerical improvement in survival that may be evident in contemporary practice as more efficacious systemic therapies for HCC are administered. Although the benefit of HCV treatment in patients with active HCC has yet to be described, these data provide rationale for consideration of HCV treatment with DAA to induce SVR for all patients with HCC who are eligible for therapy.

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AUTHOR CONTRIBUTIONS
Neeshar D. Parikh: Conceptualization, analysis, data acquisition, writing, critical revision, and guarantor of this article. Amit G. Singal: Conceptualization, analysis, data acquisition, writing, and critical revision. Matthew J. Schipper: Analysis, data acquisition, and writing. Neil Mehta: Data acquisition and critical revision. Maaranf O. Hoteit: Data acquisition and critical revision. Ju Dong Yang: Data acquisition and critical revision.Binu V. John: Data acquisition and critical revision. Andrew M. Moon: Data acquisition and critical revision. Reena J. Salgia: Data acquisition and critical revision. Anjana Pillai: Data acquisition and critical revision. Ibah Kassab: Data acquisition. Naba Saeed: Data acquisition. Emil Thyssen: Data acquisition. Piyush Nathani: Data acquisition. Jeffrey McKinney: Data acquisition. Wesley Chan: Data acquisition. Claire Durkin: Data acquisition. Matthew Connor: Data acquisition. Manaf Alshudayeny: Data acquisition. Rajesh Konjenti: Data acquisition. Brenda Durand: Data acquisition. Nicholas N. Nissen: Data acquisition. Hannah P. Kim: Data acquisition. Raghavendra Paknikar: Data acquisition. Nicole E. Rich: Data acquisition and critical revision.

CONFLICTS OF INTEREST
Neeshar D. Parikh served as a consultant for Bristol Myers-Squibb, Exact Sciences, Eli Lilly; has served on advisory boards of Genentech, Eisai, Bayer, Exelixis, and Wako/Fujifilm; and has received institutional research funding from Baylor, Target, Genentech, Exact Sciences, and Glycosteat. Neil Mehta served on the advisory boards of Exelixis and Wako/Fujifilm and has received research funding from Target, Wako/Fujifilm, and Glycosteat. Ju Dong Yang has served as a consultant for Exact Sciences, Gilead Sciences, and Eisai. Binu John has served on advisory board for Dova and has received institutional research funding from Bristol-Myers Squibb, Genentech, H3B biosciences, Glycosteat, Glaxo SmithKline, and Viking Therapeutics. Anjana Pillai currently serves on a medical advisory board for Genentech, Eisai, Exelixis, and Replimune; and is a speaker for Simply Speaking Hepatitis (CME). Reena J. Salgia has served on advisory boards for Bayer, Eisai, and Exelixis. Matthew J. Schipper has served as a consultant to Innovative Analytics. Amit G. Singal has served as a consultant or on advisory boards for Genentech, Bayer, Eisai, AstraZeneca, Exelixis, Bristol Meyers Squibb, Fujifilm Wako Diagnostics, Exact Sciences, Roche, Glycosteat, and GRAIL. Andrew M. Moon reports consulting fees for work on TARGET HCC. The other authors made no disclosures.

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DATA AVAILABILITY STATEMENT
Because of patient privacy concerns, we will not be able to share the data associated with this manuscript.

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