Editorial

JOURNAL OF HEPATOLOGY

The quest for precision oncology with immune checkpoint inhibitors for hepatocellular carcinoma

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The advent of immune checkpoint inhibitors (ICIs) has drastically changed the landscape of hepatocellular carcinoma (HCC) treatment. Nivolumab was the first ICI to receive accelerated approval from the Food and Drug Administration (FDA) in 2017 based on an objective response rate of ~15% and prolonged duration of response in patients previously treated with sorafenib.[1] These results were followed by encouraging phase II data for other ICIs – pembrolizumab monotherapy and nivolumab in combination with ipilimumab – also resulting in accelerated approvals by the FDA.[2,3] Finally, the combination of atezolizumab and bevacizumab is now established as the standard of care first-line treatment of advanced-stage HCC based on results of the IMBrave-150 trial, which showed a significantly improved overall survival (OS), progression-free survival (PFS) and quality of life compared to sorafenib.[4] Most recently, the combination of cabozantinib and atezolizumab was reported to improve PFS and durvalumab and tremelimumab was reported to improve OS compared to sorafenib in patients with unresectable HCC. Several additional clinical trials are ongoing to evaluate ICIs as monotherapy or in combination with other agents both in first- and second- lines.[5]

Despite these improvements, less than one-third of patients treated with ICIs achieve an objective response rate (ORR) and median survival for patients with advanced-stage HCC remains below 2 years.[1–4] Therefore, one of the most relevant unsolved medical needs in this field is the identification of a treatment response biomarker that can help select patients with a higher probability of response to ICIs. From a methodological point of view, one must be careful not to overinterpret small differences in subgroup analyses, particularly if not pre-planned and supported by a biological hypothesis. In contrast, effect modification occurs when the magnitude of effect of the primary exposure on an outcome significantly differs depending on the level of a third variable, *i.e.*, the effect modifier. An ideal biomarker for this goal should be simple, inexpensive, and easily measurable soon after HCC diagnosis. One of the best examples in HCC treatment has been alpha-fetoprotein (AFP) as a treatment response biomarker for ramucirumab, with high-AFP patients but not low-AFP patients achieving a survival benefit.[6] Previously, the beneficial effect of sorafenib was also shown to be greater in patients with hepatitis C infection and those who experienced hand-foot skin reaction via official moderator analyses. To date, available clinical trial data for ICIs in patients with HCC have failed to identify effect modifiers or subgroups of patients with higher likelihood of response. This is not trivial as identification of patients who respond differently is necessary to generate response-guided therapeutic algorithms and can avoid futile treatment of patients with a low chance of response. In contrast to other tumors, ICI efficacy in HCC does not seem to be related to PD-L1 expression, and treatment response biomarkers observed in other cancers such as microsatellite instability are rare in HCC.[7] In the absence of biomarkers to promote a model of precision treatment, providers have decided between different options based on differences in trial populations (*e.g.*, exclusion criteria), treatment-related adverse event (AE) profiles, secondary outcomes including ORR, and availability of real-world data in extended populations; however, these decisions are often subjective and lead to substantial variation in practice patterns.

Scheiner and colleagues address this area of need in a recent multicenter retrospective cohort study,[8] in which they developed and externally validated a biomarker panel (CRAFITY score), including C-reactive protein (CRP) ≥1 mg/dl and AFP ≥100 ng/ml, for patients receiving ICI therapy using a multiple time-fixed Cox regression model. In the external validation cohort, the CRAFITY score was able to stratify patients in terms of OS. C-statistics were 0.62 in both the derivation and validation cohorts, and the model had good calibration between predicted and observed survival probabilities. The CRAFITY score was also evaluated in a cohort of patients receiving sorafenib and was able to stratify patients in terms of OS but not disease control rate.

The CRAFITY score has several strengths including its use of 2 serum-based laboratory measures that can be easily checked, without a need for invasive histologic assessment. Despite this simplicity, the model was able to accurately stratify patients treated with ICIs in terms of OS. In contrast to sorafenib-treated patients, the potential association with disease control rate in

Keywords: liver cancer; prognosis; Immune checkpoint inhibitors.
Received 18 October 2021; received in revised form 10 November 2021; accepted 22 November 2021; available online xxx
DOI of original article: https://doi.org/10.1016/j.jhep.2021.09.035.
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https://doi.org/10.1016/j.jhep.2021.11.021

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ICI-treated patients suggests a role for CRAFITY as a treatment response biomarker and not simply as a prognostic biomarker.[9] However, whether CRAFITY is truly able to accurately predict radiological response will need to be evaluated in future studies. It is well known that higher AFP levels are associated with worse prognosis, with higher AFP levels being associated with increased recurrence after liver transplantation and worse OS among those with advanced-stage disease.[10,11] There is biological rationale for why CRAFITY may act as a treatment response biomarker for patients being treated with ICIs. With increasing recognition of HCC heterogeneity, Sia and colleagues found approximately one-fourth of HCCs have markers of an inflammatory response (immune class), including 2 subclasses characterized by adaptive or exhausted immune responses.[12] These data highlighted that some HCCs may be more susceptible to ICIs targeting the PD-1/PD-L1 axis. More recently, tissue samples from the Checkmate040 trial also demonstrated an inflammatory 4-gene signature, including CD274, CD8A, LAG3, and STAT1, was associated with improved objective responses and OS among patients treated with nivolumab.[13] CRP, a known marker of systemic inflammation, may correspond to these inflammatory pathways and a higher likelihood of an immunologically "hot tumor".[14] Further, the authors describe the association of CRP and AFP with an immunosuppressive state, involving suppression of CD4+ and CD8+ T cells, reduction in co-stimulatory signals from mature dendritic cells, inhibition of natural killer cells, and expansion of myeloid-derived suppressor cells.[15]

The study by Scheiner and colleagues is another step towards precision oncology, providing a biomarker panel that helps identify patients who are more likely to respond to ICIs. However, while the model was able to stratify patients and achieve good calibration, its c-statistic in both the derivation and validation cohorts was only 0.62, highlighting room for further improvement before its incorporation into clinical practice. Several emerging–omics approaches (such as radiomics, genomics, transcriptomics or metabolomics) could improve the selection of patients at higher probability of benefitting from ICI treatment. Future studies should aim to evaluate the additive value of the 4-gene signature, in cases where tissue is available, as well as factors associated with ICI response in other cancers such as the gut microbiome, circulating tumor DNA, and exosomal molecules.[16,17]

In addition to lower than desired discrimination, the authors acknowledge the marked heterogeneity of the cohort including different ICI therapies, lines of therapy, and liver disease severities – all of which can complicate interpretation of the observed associations. Although the authors performed subgroup analyses to evaluate some of these effects, this was done using patients from both the derivation and validation cohorts, leading to possible overfitting of the model. Finally, most of the patients in the current analysis were treated with nivolumab or pembrolizumab monotherapy, whereas recent trials have focused on combination therapies in which ICIs are combined with anti-VEGF inhibitors (*e.g.*, bevacizumab), tyrosine kinase inhibitors (*e.g.*, cabozantinib or lenvatinib), or CTLA-4 inhibitors (*e.g.*, tremelimumab or ipilimumab). Future studies will be needed to see if the CRAFITY score performs well in patients treated with combination therapies. Considering these limitations, the CRAFITY score may be considered as a stratification variable for clinical trials of ICIs but likely warrants further refinement and validation before being applied to identify patients for ICI treatment in clinical practice.

Additionally, most studies in precision oncology have focused on treatment efficacy, although safety represents another important aspect of treatment. The prognosis of patients with HCC can often be driven by a competing risk of liver-related mortality, particularly when use of ICIs is expanded to patients with more advanced liver dysfunction than the Child-Pugh A patient population typically included in clinical trials.[18] The management of patients with HCC should be guided by a risk-benefit analysis balancing treatment effectiveness and the risk of treatment-related AEs, as assessed by the incremental safety-effectiveness ratio.[19] It may be possible to similarly use a risk stratification model to differentiate ICI-treated patients at high *vs.* low risk of immune-related AEs and/or liver-related mortality.[20] Although immune-related AEs are rare with ICIs, they can be severe in nature and even fatal in cases.[21] Having data on the predicted benefits and harms in an individual could facilitate precision oncology, whereby ICIs are provided to patients with high predicted benefit and low risk of AEs but avoided in those with low benefit and high risk of AEs.

In summary, the CRAFITY score provides another tool that pushes the HCC field one step closer to a precision oncology paradigm. However, prospective studies are still needed to further optimize the performance of available treatment response biomarkers and address other remaining gaps. These studies will be critical to help determine whether the CRAFITY score, or other emerging biomarker panels, can be applied in clinical practice to guide treatment decisions and identify a subgroup of patients who would derive the greatest benefit-to-risk ratio with ICI therapy.

Financial support

AGS research supported in part by National Institutes of Health (NIH) R01 MD012565.

Conflict of interest

Giuseppe Cabibbo has served as a consultant or on advisory boards for Bayer, Eisai, and Ipsen. Amit Singal has served as a consultant or on advisory boards for Bayer, Wako Diagnostics, Exact Sciences, Roche, Glycotest, and GRAIL.

Authors' contributions

Interpretation of data and drafting of the manuscript (all authors); critical revision of the manuscript for important intellectual content (all authors). All authors approve final version of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.11.021.

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Author names in bold designate shared co-first authorship

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