Editorial Commentary

Advancing the management of hepatocellular carcinoma: surrogate markers and predictive biomarkers for survival on immunotherapy

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To extend overall survival (OS) in patients with hepatocellular carcinoma (HCC) receiving combination therapy with immune checkpoint inhibitors (ICIs), it is critical to identify patient subgroups that can maximize therapeutic benefits or those unlikely to respond effectively. Specifically, the identification of surrogate markers capable of predicting OS early after treatment initiation and biomarkers that can estimate antitumor efficacy prior to treatment initiation is of utmost importance in optimizing pharmacological therapy for HCC.

Regarding surrogate markers for OS in HCC pharmacotherapy, Kudo and colleagues previously conducted a systematic review of randomized clinical trials (RCTs) on advanced HCC (1). Using the Response Evaluation Criteria in Solid Tumors (RECIST) and its modified version (mRECIST). They evaluated whether objective response (OR) could serve as a surrogate indicator for OS. An analysis of 34 RCTs revealed significant associations between the odds ratio of OR and the hazard ratio (HR) of OS, with correlation coefficients (R) of 0.677 [95% confidence interval (CI): 0.655–0.6970] for mRECIST and 0.532 (95% CI: 0.519–0.545) for RECIST. Furthermore, a meta-analysis of five RCTs that evaluated the predictors for survival through multivariate analysis demonstrated that patients achieving OR per mRECIST had a pooled HR for OS of 0.44 (95% CI: 0.27–0.70) compared to non-responders, indicating that patients who achieve an OR tend to have better OS. These findings indicate that OR measured by mRECIST is an independent predictor of OS in the pharmacological treatment of advanced HCC and that its correlation with OS surpasses that of OR measured by RECIST. While the correlation coefficient does not reach the level required for use as a surrogate endpoint in phase III clinical trials, it is sufficient for reassessing treatment strategies based on early antitumor response determined by mRECIST, which may contribute to improved OS in real-world clinical practice (1).

Notably, the response to atezolizumab-bevacizumab combination therapy has been reported to contribute more significantly to OS than the responses achieved with tyrosine kinase inhibitors (TKIs) (1). Small molecules, such as TKIs, are prone to resistance due to the acquisition of genetic mutations or alterations in intracellular signaling pathways in cancer cells. In contrast, therapies mediated by immune mechanisms may demonstrate more durable therapeutic effects compared to TKIs, suggesting that OR achieved through ICI-based therapies is more likely to correlate with survival outcomes. Additionally, Zhu and

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colleagues focused on clinical trials investigating ICIs for advanced HCC to assess whether antitumor efficacy measured by RECIST could serve as a surrogate marker for OS (2). A meta-analysis of 26 clinical trials revealed that the OR rate was positively correlated with OS, with an R value of 0.71 (95% CI: 0.52–0.84). These findings underscore the critical importance of early antitumor response in guiding the management of immunotherapy-based treatments for HCC.

Recently, Campani *et al.* analyzed the association between antitumor response and OS using real-world data, focusing on RECIST 1.1 and mRECIST evaluations conducted through computed tomography (CT) or magnetic resonance imaging (MRI) imaging 12 weeks after initiating combination therapy with atezolizumab and bevacizumab (3). Both RECIST 1.1 and mRECIST identified that patients classified as achieving OR exhibited significantly longer OS compared to the non-OR group. Furthermore, among progression patterns, the emergence of new extrahepatic lesions or vascular invasion was associated with particularly poor OS. These findings strongly suggest that such progression patterns have a substantial impact on OS.

Regarding antitumor efficacy, both RECIST 1.1 and mRECIST evaluations showed a considerable correlation with OS. However, mRECIST, which reflects arterial blood flow reduction—a hallmark of regimens including the angiogenesis inhibitor bevacizumab—demonstrated a higher OR rate and may be considered more practical for clinical use. While sufficient interobserver agreement was observed between the two evaluations, attention should be paid to interobserver variability in assessing tumor enhancement using mRECIST. Additionally, cases judged as progressive disease (PD) via radiologic evaluation but deemed non-PD by a multidisciplinary tumor board (MDT) exhibited relatively favorable OS outcomes. MDT evaluations incorporated additional factors such as decreases in alpha-fetoprotein (AFP) (3). Previously, Zhu *et al.* analyzed data from phase I and III clinical trials (GO30140 and IMbrave150) of atezolizumab and bevacizumab, reporting that reductions in AFP levels at 6 weeks post-treatment initiation were associated with favorable OS and progression-free survival (PFS) (4) (*Figure 1*). Similarly, using real-world data, Ando *et al.* demonstrated that changes in AFP levels 3 weeks post-treatment initiation correlated with radiological response at 6 weeks (5). Therefore, early AFP reductions after the initiation of atezolizumab and bevacizumab may predict favorable antitumor response and survival outcomes. In addition to these conventional clinical indicators, molecular markers associated with OS are also being developed (6). For example, in other types of cancer, efforts have been made to quantify circulating tumor DNA (ctDNA) during treatment to assess tumor burden and use it as a surrogate marker for OS (7) (*Figure 1*). Recent advancements include the development of highly sensitive methods for the detection of ctDNA based on machine learning, with applications for real-time monitoring of the antitumor effects during treatments including those involving ICIs (8).

Similarly, numerous studies have reported the potential of clinical factors and molecular markers at treatment initiation to predict treatment response for immunotherapy in HCC. Among clinical indicators, the neutrophil-to-lymphocyte ratio (NLR) has been reported as a predictor of OR and PFS, highlighting its potential utility in guiding patient selection for atezolizumab and bevacizumab combination therapy (9,10). Additionally, the tumor immune microenvironment (TME) has been shown to influence the efficacy of ICI-based treatments (11). For example, patients with HCC who developed an immune-excluded TME and treatment resistance during atezolizumab and bevacizumab therapy have been reported (12). In recent years, pathological and omics analyses have been conducted to explore alterations in cancer-related genes and molecules involved in the specific TME as potential biomarkers for the treatment of HCC (6) (*Figure 1*).

Shi *et al.* conducted a study involving 1,125 HCC patients from the Zhongshan cohort (China) and 320 patients from The Cancer Genome Atlas (TCGA) cohort (13). They utilized deep learning models, specifically ResNet-50, to extract image features from hematoxylin and eosin (H&E)-stained pathological slides, enabling the identification of tumor tissue, normal tissue, stroma, and necrotic regions. A weakly supervised deep learning model was employed to calculate a tumor risk score (TRS) using tile images of the tumor tissue. The association between TRS and tumor immune infiltration, as well as genetic mutations, was analyzed. TRS was identified as an independent prognostic factor for postoperative HCC survival in both cohorts, demonstrating superior prognostic accuracy compared to conventional TNM and Barcelona Clinic Liver Cancer (BCLC) classifications. Notably, high TRS was associated with distinct pathological features, including sinusoidal capillarization, a decrease in $CD4^+$ memory T cells and effecter T cell (Teff), and an increase in neutrophil, M0

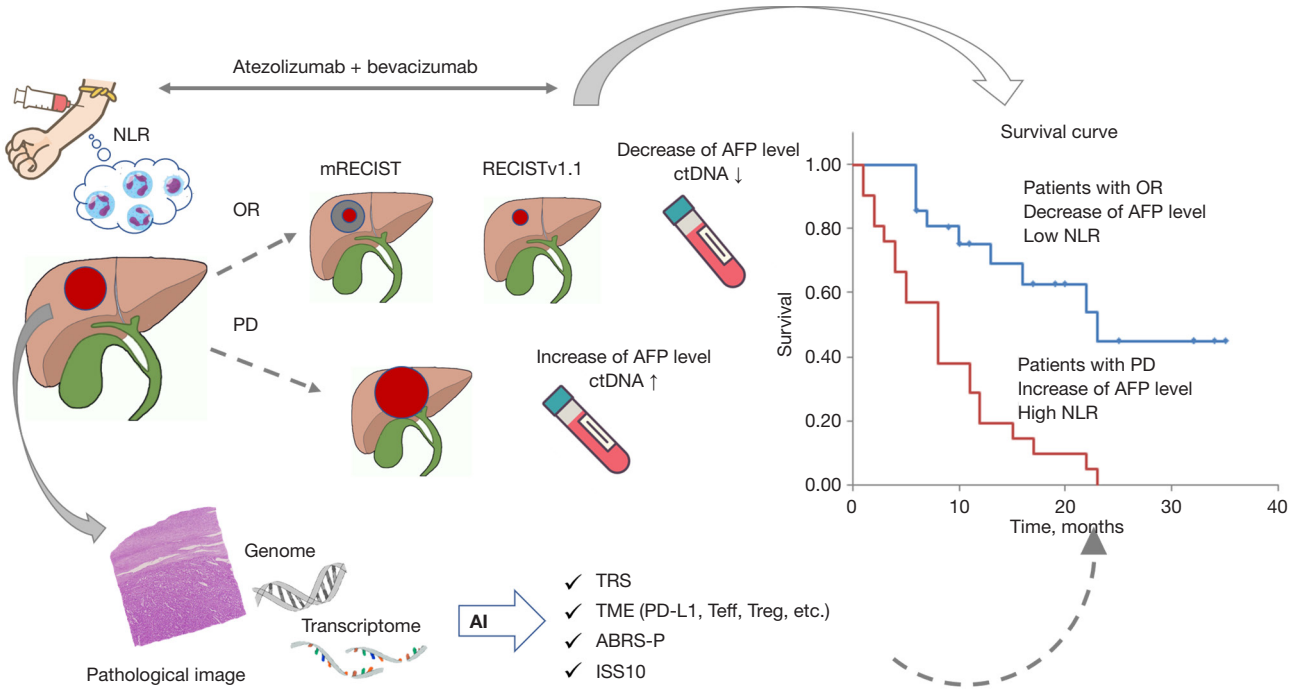

Figure 1 Application of surrogate markers and predicting biomarker for survival in immunotherapy of hepatocellular carcinoma. Early radiological response to atezolizumab plus bevacizumab combination therapy is reportedly associated with OS. Therefore, in cases of insufficient antitumor response, reconsideration of the therapeutic regimen may be necessary. Additionally, an early decline in AFP levels is correlated with favorable antitumor response and OS. In addition, efforts have also been made to utilize changes in ctDNA levels during treatment as a marker of tumor dynamics. Moreover, it is also reported that a lower NLR at the initiation of treatment has been linked to improved OS. Other promising biomarkers for predicting antitumor efficacy include the TRS, which is calculated based on pathological findings of tumor tissue, and estimations of the TME derived from omics analyses of tumor tissue. Furthermore, artificial intelligence algorithms based on omics data have been used to develop predictive score for survival such as the ABRS-P and the ISS10. These biomarkers hold promise for guiding decisions for treatment and optimizing the outcome of immunotherapy. AFP, alpha-fetoprotein; ABRS-P, Atezolizumab-Bevacizumab Response Signature-Prediction; ctDNA, circulating tumor DNA; ISS10, immune signature scores 10; mRECIST, modified response evaluation rriteria in solid tumors; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; OR, objective response; PD, progressive disease; PD-L1, programmed cell death-ligand 1; Teff; effector T cell; Treg; regulatory T cell; TRS, tumor risk score; TME, tumor immune microenvironment.

macrophage, and regulatory T cell (Treg) infiltration—findings suggestive of alterations in angiogenesis and antitumor immunity (13). Although this study focused on the relationship between TRS and postoperative survival in HCC and did not evaluate responsiveness to pharmacological therapies, including ICIs, the methodology employed holds promise for biomarker development in HCC treatment, particularly in predicting responses to ICIs and other systemic therapies.

Analyses of data from the GO30140 and IMbrave150 clinical trials revealed that TME states, such as PD-L1 expression, Teff signatures based on transcriptome analyses, and the dense infiltration of intratumoral $CD8^+$ T cells, were associated with favorable antitumor responses (14). Conversely, cases with high Treg-to-Teff ratios or high expression of oncofetal proteins showed limited clinical benefit from ICIs. Furthermore, pathological image data from these clinical trials have been linked with the results from omics analyses and utilized as training data for the development of artificial intelligence (AI) (15). This approach has facilitated the development of a predictive AI model, the Atezolizumab-Bevacizumab Response Signature-Prediction (ABRS-P), which predicts response to combination therapy with atezolizumab and bevacizumab

based on the pathological images (15). Transcriptome analyses of the GO30140 and IMbrave150 cohorts have also led to the development of another prediction algorithm, immune signature scores 10 (ISS10)—predictive models based on a smaller set of genes—to estimate response to combination therapy (16,17).

Predicting therapeutic efficacy, particularly OS, prior to initiating pharmacological treatment for HCC remains a significant challenge in clinical settings. Currently, no biomarker has been firmly established for this purpose, representing an unmet need in HCC treatment. In clinical practice, there is a pressing need to use indicators associated with OS early after treatment initiation as a guide for pharmacological therapy. Alongside biomarker development, it is crucial to collect large-scale real-world data to build clinical evidence for surrogate marker of survival that facilitate effective pharmacological interventions.

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