SUPPLEMENTAL METHODS

Public data collection and preparation

All clinical and raw RNA-seq data for the GO30140 and IMbrave150 trials were downloaded from the European Genome-phenome Archive (EGA, https://ega-archive.org/) under accession number EGAS00001005503. This dataset includes RNA-seq FASTq files for 181 bulk pre-treatment and 14 post-treatment tumors from GO30140 Phase 1b groups A and F, as well as 177 bulk pre-treatment tumors from the IMbrave150 Phase III trial. This comprehensive dataset reveals molecular correlates of clinical response and resistance to Atezolizumab plus Bevacizumab and Sorafenib in advanced hepatocellular carcinoma. Patients with post-treatment tumors were excluded, resulting in 253 patients in the Atezolizumab plus Bevacizumab treatment arm and 58 patients in the Sorafenib treatment arm.

Curation of immunotherapy response predictive signatures (IRPS)

We conducted an extensive literature review of studies published in recent years to compile a state-of-the-art set of signatures in immunotherapy. Keywords such as “immune checkpoint blockade/immunotherapy”, “PD-1/PD-L1”, “biomarker/signature”, “prediction/predictor”, and “response” were used in our search. The abstracts and results sections (if necessary) were carefully examined, and signatures exhibiting predictive potential for immunotherapy response were included. Ultimately, we collected a total of 23 transcriptomic signatures considered to be indicators of immune checkpoint blockade (ICB) response (Supplementary Table 1). The gene symbols were cleaned and transformed using the checkGeneSymbols function from HGNChelper package to identify outdated or Excel-mogrified gene symbols before being subjected to downstream analysis. The “CHIANG_LIVER_CANCER_SUBCLASS_PROLIFERATION_UP” gene set from the Molecular Signatures Database (MSigDB) was utilized to calculate the aggressive score for HCC.

Defining high and low signature subtypes

The signature activity was defined using the Single-Sample Gene Set Enrichment Analysis (ssGSEA) score of all the genes in the gene set. ssGSEA, an extension of GSEA, calculates separate enrichment scores for each pairing of a sample and gene set. The ssGSEA score was calculated using the Bioconductor GSVA package with the curated gene signatures. The high and low signature subtypes were stratified based on the median ssGSEA score.

Identification of atezolizumab plus bevacizumab response predictive signatures (ABRPS)

The Atezolizumab plus Bevacizumab Response Predictive Signatures (ABRPS) were defined as molecular signatures that categorize patients into high or low subtypes. These subtypes exhibited statistically significant differences in both overall survival (OS) and progression-free survival (PFS) when treated with atezolizumab and bevacizumab, compared to sorafenib. These differences should be validated using both the Cox proportional hazards model and the log-rank test.

HR score definition and calculation

The hazard ratio (HR) score was used to evaluate the predictive performance of the 23 immunotherapy response predictive signatures, with a higher HR score indicating superior predictive performance. The HR score was defined as the absolute difference between the HR values of high and low signature scores and was calculated using the following formula: HR score=|HR_high - HR_low|.

Survival analysis

We performed survival analysis using median values as cut-offs for continuous variables. Kaplan–Meier methods were employed to carry out the survival analysis, and the log-rank test was used to determine the statistical significance of differences. The HR was estimated using a Cox regression model with the survival R package. Univariate survival analyses were performed using the Cox proportional hazards regression model. The survival curve was generated using the R survminer package.

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Statistical analysis

Qualitative data were analyzed using Pearson's Chi-Square or Fisher's exact test as appropriate. Survival curves were estimated by the Kaplan–Meier method, and the log-rank test was used to determine the statistical differences between survival curves. Statistical analysis and data visualization were carried out using the R/Bioconductor software packages. A two-sided *P*-value of less than 0.05 was considered statistically significant for all analyses.