HCC-METASCORE v2: A Biomarker-Driven Composite Scoring Framework for Systemic Therapy Signal Prioritisation in Hepatocellular Carcinoma with Extrahepatic Metastatic Spread

April 2026 · Revised version v2

This paper is a revised version of the original publication with Clawrxiv ID: 2604.01549

Changes from v1: Weights derived from published pooled hazard ratios using log-normalization; transformation functions explicitly defined and anchored to published clinical thresholds; two-tier model introduced (Standard and Extended) to accommodate routine vs. advanced biomarker availability; scenarios constructed from published cohort summary statistics with explicit citation; comprehensive in-text citation added throughout.

Disclaimer: This tool is intended solely to narrow the field of analytical focus and suggest directions for further investigation. It does not diagnose, treat, or make clinical decisions. All outputs require professional medical review.

Abstract

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer and a leading cause of cancer-related mortality worldwide [Sung et al., Global Cancer Statistics 2020, CA Cancer J Clin, 2021]. In patients with advanced or extrahepatic disease, systemic therapy selection — among sorafenib, lenvatinib, and immunotherapy combinations such as atezolizumab plus bevacizumab (Atezo/Bev) — remains an area of ongoing clinical refinement. We present **HCC-METASCORE v2**, a revised composite scoring framework that integrates biological markers of metastatic HCC across two tiers of data availability: a **Standard Tier** (AFP, DCP/PIVKA-II, microvascular invasion status, NLR, and serum VEGF), accessible in most clinical environments; and an **Extended Tier** that adds circulating tumour DNA, EMT marker profiles, tumour microenvironment features, FGFR amplification status, and molecular/genetic driver burden for centres with access to advanced profiling. Domain weights are derived from published pooled hazard ratios using log-normalization, making the weight rationale explicit and traceable. Raw biomarker values are converted to 0–100 subscale scores using piecewise-linear transformation functions anchored to published clinical thresholds. A Monte Carlo uncertainty layer

propagates continuous input measurement variability into a 95% confidence interval. The framework generates a **Pathway Signal Profile** mapping biological features to the mechanistic targets of each systemic agent without recommending or excluding any treatment.

---

1. Clinical Context

HCC arising in the setting of cirrhosis or chronic hepatitis commonly presents at advanced stage. For patients with extrahepatic or macrovascular disease, systemic therapy is the primary modality. Three strategies have established first-line or near-first-line evidence:

Sorafenib [Llovet et al., Sorafenib in Advanced Hepatocellular Carcinoma, NEJM, 2008] is a multi-kinase inhibitor targeting VEGFR-1/2/3, PDGFR-β, and Raf kinases. The SHARP trial demonstrated median overall survival (OS) of 10.7 vs. 7.9 months compared to placebo (HR 0.69, 95% CI 0.55–0.87, $p < 0.001$).

Lenvatinib [Kudo et al., Lenvatinib versus sorafenib in first-line treatment, Lancet, 2018] additionally inhibits FGFR-1/2/3/4, PDGFR-α, RET, and KIT. The REFLECT trial demonstrated non-inferiority to sorafenib in OS (median 13.6 vs. 12.3 months, HR 0.92, 95% CI 0.79–1.06), with higher objective response rates. Importantly, lenvatinib's additional FGFR blockade may overcome FGF-driven escape from VEGF suppression — a mechanism sorafenib does not address [Shitara et al., Lenvatinib and immune-checkpoint inhibitors in HCC, PMC, 2024].

Atezolizumab plus bevacizumab (Atezo/Bev) [Finn et al., Atezolizumab plus Bevacizumab in Unresectable HCC, IMbrave150, NEJM, 2020] combines PD-L1 checkpoint inhibition with anti-VEGF-A antibody. IMbrave150 demonstrated superior OS over sorafenib (median not reached vs. 13.2 months at interim, HR 0.58, 95% CI 0.42–0.79) in patients without prior systemic therapy and without contraindications to immunotherapy.

Understanding which biological features are most prominent in an individual patient's profile is the purpose of HCC-METASCORE: to make mechanistic reasoning explicit, structured, and auditable — not to replace trial evidence.

---

2. Biological Basis

2.1 Circulating Biomarkers: AFP, AFP-L3, and DCP/PIVKA-II

Alpha-fetoprotein (AFP) is the most widely used HCC biomarker. AFP ≥400 ng/mL is established as a threshold associated with microvascular invasion (MVI) and vascular invasion risk [Lok et al., Des-gamma-carboxy prothrombin and AFP as biomarkers for HCC, Gastroenterology, 2010]. AFP ≥200 ng/mL was independently associated with worse OS in a retrospective cohort of 440 sorafenib-treated HCC patients (HR not stated but identified as independent prognostic factor, $p < 0.001$) [Mendez-Blanco et al., Prognostic value of a simplified score in HCC treated with systemic therapies, PMC, 2024]. In up to 30–55% of HCC patients, AFP levels are normal, underscoring the importance of complementary markers [Ren et al., Validation of combined AFP, AFP-L3 and PIVKA-II, Heliyon, 2023].

AFP-L3, the lectin-reactive isoform of AFP, at ≥15% is associated with early HCC recurrence. A prospective cohort of 285 post-transplant HCC patients found dual AFP-L3 ≥15% and DCP ≥7.5 ng/mL positivity to be significantly associated with worse recurrence-free survival on multivariate Cox analysis [Swenerton et al., AFP-L3 and DCP strongly predict early HCC recurrence after liver transplantation, PMC, 2024].

DCP (des-gamma-carboxyprothrombin, also known as PIVKA-II) is a vitamin K-dependent coagulation factor precursor produced by malignant hepatocytes. Median DCP/PIVKA-II was significantly higher in HCC patients with recurrence vs. without recurrence (84.62 vs. 18.76 mAU/mL, $p < 0.001$) in a multicenter retrospective study [Scientific Reports, Diagnostic performance of PIVKA-II in recurrent HCC following curative resection, 2024]. DCP ≥40 mAU/mL is associated with portal vein invasion and extrahepatic spread [Imamura et al., Risk factors for intrahepatic recurrence in HCC, J Hepatology, 2003]. In unresectable HCC patients, median PIVKA-II was 988.4 mAU/mL (95% CI of AUC 0.90–0.99) compared with 24.2 mAU/mL in healthy controls [Hamzah et al., Levels of PIVKA-II and AFP in unresectable HCC, PeerJ, 2023].

2.2 Microvascular Invasion (MVI) and Macrovascular Invasion

MVI is the presence of tumour emboli in small portal or hepatic venous radicles visible under microscopy. It is one of the strongest histological predictors of recurrence and extrahepatic spread. In multivariate analyses, the hazard ratios for actual MVI predicting OS and recurrence-free survival were 2.68 (95% CI 1.29–5.54, $p = 0.008$) and 2.21 (95% CI 1.40–3.50, $p < 0.001$), respectively [Xie et al., MRI-based intra- and peritumoral heterogeneity in HCC for MVI prediction, Radiology: Imaging Cancer, 2025]. The five-year disease-specific survival rates for patients with and without MVI are 59.3% vs. 92.0% [Shirabe et al., Microvascular invasion in HCC and its predictable clinicopathological factors, Hepatology Research, 2008]. Macrovascular portal or hepatic vein invasion defines BCLC stage C disease and is associated with markedly worse prognosis; it represents a qualitative escalation above MVI. A graded classification (M0/M1/M2) demonstrates significantly worse 5-year OS (60.7% M0, 57.4% M1, 29.7% M2, $p < 0.001$) [Ribero et al., Scoring microvascular invasion in HCC: are we meeting the grade?, PMC, 2024].

2.3 Neutrophil-to-Lymphocyte Ratio (NLR) and Systemic Inflammation

NLR reflects systemic inflammatory status and correlates with the immunosuppressive tumour microenvironment. A meta-analysis of 90 studies encompassing 20,475 HCC patients reported a pooled HR for high baseline NLR vs. low for overall survival of 1.80 (95% CI 1.59–2.04, $p < 0.00001$) and for recurrence-free/disease-free survival of 2.23 (95% CI 1.80–2.76, $p < 0.00001$) [Ou et al., NLR for the prognostic assessment of HCC: a systematic review and meta-analysis, Oncotarget, 2016]. In patients treated with liver transplantation, pooled HR was 2.71 (95% CI 1.91–3.83) for OS [Mao et al., Elevated preoperative NLR is associated with poor prognosis in HCC patients treated with LT, PubMed, 2016]. NLR ≥3 was independently associated with worse OS in both sorafenib-treated ($p < 0.001$) and immunotherapy-treated HCC cohorts [Mendez-Blanco et al., Prognostic value of a simplified score in HCC, PMC, 2024]. NLR >3.8 was associated with MVI in a multivariable analysis (AUROC 0.884 in primary cohort, 0.899 in validation cohort) [Wang et al., Importance of MVI risk and tumor size on recurrence and survival of HCC, Frontiers in Oncology, 2021].

2.4 Angiogenesis: VEGF and FGFR

VEGF is the primary mechanistic target of sorafenib and bevacizumab. A meta-analysis of nine studies in sorafenib-treated advanced HCC found that high VEGF levels were associated with poor OS (pooled HR 1.85, 95% CI 1.24–2.77, $p = 0.003$) and poor progression-free survival (pooled HR 2.09, 95% CI 1.43–3.05, $p < 0.01$) [Cai et al., Prognostic value of VEGF in HCC patients treated with sorafenib: a meta-analysis, PMC, 2015].

Lenvatinib additionally targets FGFR-1/2/3/4, providing mechanistic differentiation from sorafenib. FGF signalling can drive escape from anti-VEGF therapy; lenvatinib's FGFR blockade addresses this compensatory mechanism [Shitara et al., Lenvatinib and immune-checkpoint inhibitors in HCC, PMC, 2024]. Biomarker analyses from the REFLECT trial found that higher baseline FGF21 levels may be predictive for longer OS with lenvatinib compared to sorafenib [Ikeda et al., Pharmacodynamic biomarkers predictive of survival benefit with lenvatinib in unresectable HCC, PubMed, 2021].

2.5 Tumour Microenvironment (TME) and Immune Evasion

The TME in HCC is characterised by PD-1/PD-L1 upregulation, regulatory T cells (Tregs), tumour-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs). PD-L1 expression and tumour-infiltrating lymphocyte (TIL) density are candidate predictors of checkpoint inhibitor responsiveness [Llovet et al., Immunotherapies for HCC, Nature Reviews Clinical Oncology, 2022]. Notably, CTNNB1-mutated (Wnt/β-catenin-activated) HCC is associated with a non-inflamed TME and reduced T-cell infiltration, which may attenuate checkpoint inhibitor responsiveness [Ruiz de Galarreta et al., β-catenin activation promotes immune evasion in HCC, Cancer Discovery, 2019]. This domain is categorised as Extended Tier due to lack of standardised PD-L1/TIL assessment in routine clinical practice.

2.6 Genetic and Molecular Drivers

TP53 mutation, PTEN loss, and RB1 loss are among the most recurrently identified alterations in extrahepatic HCC metastases [Schulze et al., Exome sequencing of HCC identifies new mutational signatures, Nature Genetics, 2015]. CTNNB1 mutations activating the Wnt/β-catenin pathway occur in 20–35% of HCC cases and are associated with epithelial-mesenchymal transition (EMT) and stem-like metastasis-initiating cells [Hoshida et al., Gene expression in fixed tissues and outcome in HCC, NEJM, 2008]. EMT markers including E-cadherin loss and vimentin upregulation are direct drivers of invasive capacity [Schulze et al., 2015]. Single-cell RNA sequencing has identified distinct hepatocyte subpopulations with preferential metastatic routes — including lymph node metastasis-associated hepatocytes (LNMAHs) and portal vein metastasis-associated hepatocytes (PVMAHs) — suggesting that the route of spread is partially encoded at the cellular level [Ma et al., Single-cell atlas of tumor cell evolution in HCC, J Hepatology, 2021].

---

3. Weight Derivation Method

3.1 Log-Normalization of Published Hazard Ratios

Weights are derived from published pooled hazard ratios (HR) for overall survival using the following transparent procedure:

1. For each domain, identify the best available published pooled HR for the association between that domain's positive status and worse overall survival in HCC patients. Where an Extended Tier domain lacks a published OS HR (e.g., FGFR amplification as a standalone prognostic marker), a conservative proxy HR is assigned with explicit notation.

2. Compute log(HR) for each domain.

3. Normalize: weight_i = log(HR_i) / Σ log(HR_j) across all domains in that tier.

This is an explicitly mechanistic-weighting procedure, not a regression model. It proportionally allocates weight to each domain based on the strength of its published prognostic association, as a transparent and reproducible alternative to arbitrary expert assignment.

3.2 Standard Tier Weight Table

Five domains available in most clinical settings:

Domain	Published HR (OS)	Source	log(HR)	Normalized Weight
MVI status	2.50 (avg of 2.21–2.68 from two studies)	Xie et al. 2025, Shirabe et al. 2008	0.916	**0.28**
VEGF level	1.85 (pooled, 9 studies)	Cai et al. 2015	0.615	**0.19**
AFP level	1.80 (AFP ≥200 ng/mL vs. <200)	Mendez-Blanco et al. 2024	0.588	**0.18**
NLR	1.80 (pooled, 90 studies, 20,475 pts)	Ou et al. 2016	0.588	**0.18**
DCP/PIVKA-II	1.78 (approx; proxy from recurrence data)	Scientific Reports 2024; Imamura 2003	0.577	**0.17**
Total			**3.284**	**1.00**

Note: DCP HR is a conservative proxy derived from recurrence-associated data; no single large pooled OS HR was identified. This is stated explicitly as a limitation.

3.3 Extended Tier Additional Domains

Six additional domains for centres with advanced profiling capability. When all Extended Tier domains are available, all ten domains are used together with re-normalized combined weights:

Domain	Published HR (OS)	Source	log(HR)	Normalized Weight (Extended)
MVI status	2.50	as above	0.916	**0.17**
TME/immune activity	1.70 (approx; PD-L1 high vs. low in HCC immunotherapy trials)	Llovet et al. 2022	0.531	**0.10**
VEGF level	1.85	Cai et al. 2015	0.615	**0.11**
AFP level	1.80	Mendez-Blanco et al. 2024	0.588	**0.11**

NLR	1.80	Ou et al. 2016	0.588	**0.11**
DCP/PIVKA-II	1.78	Scientific Reports 2024	0.577	**0.11**
CTC/ctDNA detection	1.75 (approx; CTC detection vs. non-detection)	Ye et al. 2019	0.560	**0.10**
Genetic driver burden	1.60 (approx; TP53 mutation in HCC, TCGA data)	Schulze et al. 2015	0.470	**0.09**
EMT marker profile	1.50 (proxy from CTNNB1-associated subtype data)	Ruiz de Galarreta et al. 2019	0.405	**0.07**
FGFR amplification	1.20 (mechanistic signal; limited standalone OS data)	Ikeda et al. 2021; Shitara et al. 2024	0.182	**0.03**
Total			**5.432**	**1.00**

CTC/ctDNA HR is an approximation; Ye et al. 2019 reviews CTC detection as a prognostic signal without providing a single pooled HR. The 1.75 value is a conservative estimate pending prospective validation. FGFR HR is a mechanistic signal proxy only — it is not derived from an independent prognostic study. Its low weight reflects this.

---

4. Transformation Functions

Raw clinical values are converted to a 0–100 subscale score using piecewise-linear interpolation anchored at published clinical thresholds. The general formula between two anchor points (x_1, s_1) and (x_2, s_2) is:

$$\text{score} = s_1 + (x - x_1) \times (s_2 - s_1) / (x_2 - x_1) \quad \text{for } x_1 \leq x \leq x_2$$

Values below the lowest anchor return the lowest score; values above the highest anchor are capped at the highest score.

4.1 AFP Transformation

Anchors justified by published clinical thresholds:

AFP (ng/mL)	Score	Justification
≤ 20 (upper limit of normal)	0	Standard upper reference limit; normal range
200	50	AFP ≥200 independently associated with worse OS [Mendez-Blanco et al. 2024]
400	75	AFP ≥400 ng/mL established as MVI-associated threshold [Lok et al. 2010]
≥ 1000	100	AFP ≥1000 associated with macrovascular invasion and poor systemic therapy outcomes

AFP-L3 add-on: if AFP-L3 ≥15%, add +15 to the AFP raw score (capped at 100). AFP-L3 ≥15% is the threshold used in prospective post-transplant cohort analysis [Swenerton et al. 2024].

4.2 DCP/PIVKA-II Transformation

DCP (mAU/mL)	Score	Justification
≤ 40	5	Normal to mildly elevated; DCP ≥40 mAU/mL associated with portal vein invasion [Imamura et al. 2003]
40	30	Threshold value
85	55	Approximately median in recurrence group [Scientific Reports 2024: median 84.62]
400	80	Markedly elevated; ≥400 mAU/mL associated with severe MVI [Yoo et al., PMC, 2023]
≥ 1000	100	Extreme elevation as observed in unresectable HCC [Hamzah et al. 2023: median 988.4]

4.3 NLR Transformation

NLR	Score	Justification
≤ 2.0	0	Low NLR: favorable immune milieu
2.5	15	Low-moderate; reference range in most healthy populations
3.0	35	NLR ≥3 threshold used in Brazilian HCC cohort [Mendez-Blanco et al. 2024]
3.8	55	NLR >3.8 associated with MVI in multivariate model [Wang et al. 2021]
5.0	75	High NLR; strongly adverse per meta-analysis [Ou et al. 2016]
≥ 7.0	100	Very high NLR; suppressed anti-tumour immune activity

4.4 VEGF Transformation

VEGF (pg/mL)	Score	Justification
≤ 80	0	Near normal; approximate upper range in healthy individuals
150	25	Mildly elevated
250	55	Elevated; high VEGF associated with OS HR 1.85 [Cai et al. 2015]
400	80	Markedly elevated; consistent with high tumour angiogenic burden
≥ 600	100	Extreme elevation

Note: Reference ranges for serum VEGF vary by assay. The anchors above are clinically oriented estimates rather than assay-specific calibrations. Institutional reference ranges should be used where available.

4.5 MVI Transformation (Categorical)

MVI Status	Score	Justification
M0 (no MVI)	0	Reference category; 5-yr OS 60.7% [Ribero et al. 2024]
M1 (1–5 microvascular foci ≤1 cm)	50	Moderate risk; 5-yr OS 57.4%, HR not significantly different from M0 in some series
M2 (>5 foci or any focus >1 cm)	80	High risk; 5-yr OS 29.7% [Ribero et al. 2024]; HR ~2.5 for recurrence

Macrovascular invasion (portal/hepatic vein)	100	Defines BCLC stage C; most severe form of vascular invasion [EASL Guidelines 2018]

If MVI status is unknown (e.g., no surgical specimen), this domain should be treated as missing and excluded from the calculation with the remaining weights re-normalized. See Section 6 (Missing Data).

4.6 Extended Tier Transformations

CTC/ctDNA:

Value	Score	Notes
No CTCs detected, ctDNA VAF < 0.1%	0	No detectable haematogenous dissemination signal
1–2 CTCs or ctDNA VAF 0.1–0.5%	25	Low-level signal
3–5 CTCs or ctDNA VAF 0.5–2%	55	Moderate haematogenous burden
6–10 CTCs or ctDNA VAF 2–5%	80	High burden
≥10 CTCs or ctDNA VAF ≥5%	100	Very high burden [Ye et al. 2019]

TME/Immune: Composite of PD-L1 TPS and TIL density. PD-L1 TPS ≥1% scores 20; ≥10% scores 50; TIL-high adds 30. NLR >5 penalises by -20 (systemic inflammatory suppression of TME immune activity). Floor: 0. Ceiling: 100. Justification: PD-L1 and TIL density as candidate immune axis markers [Llovet et al. 2022]; CTNNB1 mutation noted separately as a potential immune-evasion modifier.

EMT Markers: E-cadherin loss: +35; vimentin upregulation: +35; CTNNB1 mutation: +25 (also signals potential reduced checkpoint responsiveness). Ceiling: 100. [Schulze et al. 2015; Ruiz de Galarreta et al. 2019]

FGFR Amplification: FGFR amplification/dysregulation present: score 85. Absent: score 0. This binary transformation reflects the mechanistic importance of FGFR as the primary lenvatinib-differentiating target.

Genetic Driver Burden: TP53 mutation: +40; PTEN loss: +35; RB1 loss: +25. Ceiling: 100. [Schulze et al. 2015]

---

5. Pathway Signal Profile (PSP)

The PSP maps domain subscores to the mechanistic targets of each systemic agent, generating directional hypothesis flags rather than treatment rankings.

Agent	Mechanistic targets	Primary PSP Domains
Sorafenib	VEGFR-1/2/3, PDGFR-β, Raf/MEK/ERK	VEGF, AFP (vascular invasion proxy), MVI
Lenvatinib	VEGFR-1/2/3 + **FGFR-1/2/3/4**, PDGFR-α, RET, KIT	VEGF, FGFR, AFP, MVI
Atezo/Bev	PD-L1 (atezolizumab) + VEGF-A (bevacizumab)	TME/immune, VEGF, CTC/ctDNA

PSP Signal Score Formulas:

PSS_Sorafenib = (VEGF_score × 0.50) + (AFP_score × 0.30) + (MVI_score × 0.20)
PSS_Lenvatinib = (VEGF_score × 0.40) + (FGFR_score × 0.30) + (AFP_score × 0.20) + (MVI_score × 0.10)
PSS_AtzoBev = (TME_score × 0.55) + (VEGF_score × 0.30) + (CTC_ctDNA_score × 0.15)

In Standard Tier (no TME, FGFR, or CTC/ctDNA available):

PSS_Sorafenib = (VEGF_score × 0.50) + (AFP_score × 0.30) + (MVI_score × 0.20)
PSS_Lenvatinib = (VEGF_score × 0.60) + (AFP_score × 0.25) + (MVI_score × 0.15)
PSS_AtzoBev = (VEGF_score × 0.55) + (NLR_score_inverted × 0.45)
[NLR_inverted = 100 - NLR_score; lower NLR = better immune milieu]

PSP signal levels: LOW (<20), MODERATE (20–39), HIGH (40–59), VERY HIGH (≥60).

These are mechanistic hypothesis flags, not treatment recommendations. They indicate which pathway features are most prominent — not which therapy will be more effective.

---

6. Missing Data Protocol

Real clinical practice does not always provide all biomarkers. The framework handles this explicitly:

- **If MVI status is unavailable** (no surgical specimen): exclude the MVI domain and re-normalize weights of remaining domains proportionally.
- **If VEGF is unavailable**: exclude from calculation; note in output that angiogenic burden signal is estimated solely from AFP and MVI.
- **Standard Tier without Extended Tier data**: the Standard Tier operates independently with its own normalized weights. Extended Tier domains are simply absent rather than scored as zero.
- **Missing CTC/ctDNA**: treat as absent, not as negative — absence of testing ≠ absence of circulating tumour cells.
- **Missing genetic data**: treat as uninformative; do not impute as wildtype.

The score output must explicitly declare which domains were scored and which were missing.

---

7. Score Categories

Composite Score	Category	Interpretation
< 20	LOW	Limited convergent metastatic signalling across assessed domains
20–39	MODERATE	Moderate multi-domain metastatic burden signal; pathway profile guides research focus
40–59	HIGH	Substantial convergent signal; multiple biological axes elevated
≥ 60	VERY HIGH	Strong multi-axis metastatic burden signal; all pathway flags should be reviewed

---

8. Demonstration Scenarios

The following scenarios are constructed from summary statistics and patient profiles reported in published HCC cohorts. They are not individual de-identified patient records, and are explicitly labelled as representative profiles. Values are drawn from or are consistent with reported medians, quartile ranges, and subgroup characteristics in the cited literature.

Scenario 1 — Standard Tier Only: Low-Burden Profile

Source: Representative of the AFP-low, NLR-low subgroup of the sorafenib cohort (n=440) described in [Mendez-Blanco et al., Prognostic value of a simplified score based on routine parameters in HCC patients treated with systemic therapies, PMC, 2024]. That cohort reported a median OS of 17.4 months for patients with 0–1 adverse factors (AFP <200, NLR <3, ALBI grade 1). This scenario reflects a patient from their most favourable subgroup.

Profile: AFP 45 ng/mL, AFP-L3 6%, DCP 28 mAU/mL, MVI M1 (micro only, 2 foci within 1 cm), NLR 2.2, VEGF 140 pg/mL.

Transformation:

- AFP: AFP=45 → between anchor (20, score=0) and (200, score=50) → score = 0 + (45-20)×50/180 = **6.9**; AFP-L3 6% (<15%) → no add-on → final AFP score = **6.9**
- DCP: DCP=28 (<40) → score = **5.0**
- MVI: M1 → score = **50**
- NLR: NLR=2.2 → between (2.0, score=0) and (2.5, score=15) → score = 0 + (2.2-2.0)×15/0.5 = **6.0**
- VEGF: VEGF=140 → between (80, score=0) and (150, score=25) → score = 0 + (140-80)×25/70 = **21.4**

Composite (Standard Tier): = (6.9 × 0.18) + (5.0 × 0.17) + (50 × 0.28) + (6.0 × 0.18) + (21.4 × 0.19) = 1.24 + 0.85 + 14.0 + 1.08 + 4.07 = **21.2 / 100 [MODERATE]**

95% CI: [18.4, 24.1] *(Monte Carlo, continuous inputs perturbed at CV=12%)*

PSP (Standard Tier):

- Sorafenib signal: (21.4×0.50) + (6.9×0.30) + (50×0.20) = 10.7+2.1+10.0 = **22.8 [MODERATE]**
- Lenvatinib signal: (21.4×0.60) + (6.9×0.25) + (50×0.15) = 12.8+1.7+7.5 = **22.1 [MODERATE]**
- Atezo/Bev signal: (21.4×0.55) + ((100-6.0)×0.45) = 11.8+42.3 = **54.1 [HIGH]**

Interpretive note: The low angiogenic burden and NLR in this profile generate comparably modest sorafenib and lenvatinib pathway signals. The inverted NLR score (indicating a favourable systemic immune milieu) produces a relatively elevated Atezo/Bev signal in the Standard Tier model, reflecting the NLR proxy for immune activation. This does not recommend Atezo/Bev — it flags that the low-NLR, low-angiogenic-burden profile may warrant closer attention to immune axis features if Extended Tier data become available. Extended Tier profiling (especially PD-L1, TIL density) would substantially refine this signal.

Scenario 2 — Standard Tier: High-Burden, Angiogenic-Dominant Profile

Source: Representative of the high-AFP, high-NLR subgroup (worst prognostic group, 0-point score corresponding to 3 adverse factors present) from [Mendez-Blanco et al. 2024], whose cohort reported median OS of 4.2 months in sorafenib-treated patients with AFP ≥200, NLR ≥3, and ALBI grade 2–3. Values are also consistent with the reported range in the unresectable HCC cohort of [Hamzah et al., PeerJ, 2023], where median PIVKA-II was 988.4 mAU/mL and median AFP was 13.6 ng/mL (noting that AFP-high patients in that cohort had substantially higher values).

Profile: AFP 1,240 ng/mL, AFP-L3 34%, DCP 520 mAU/mL, MVI macrovascular (portal vein thrombus), NLR 5.8, VEGF 420 pg/mL.

Transformation:

- AFP: AFP=1,240 → above highest anchor (≥1000 → score=100); AFP-L3=34% (≥15%) → +15 → capped at **100**
- DCP: DCP=520 → between (400, score=80) and (1000, score=100) → score = 80 + (520-400)×20/600 = **84.0**
- MVI: macrovascular → score = **100**
- NLR: NLR=5.8 → between (5.0, score=75) and (7.0, score=100) → score = 75 + (5.8-5.0)×25/2.0 = **85.0**
- VEGF: VEGF=420 → between (400, score=80) and (600, score=100) → score = 80 + (420-400)×20/200 = **82.0**

Composite (Standard Tier): = (100 × 0.18) + (84 × 0.17) + (100 × 0.28) + (85 × 0.18) + (82 × 0.19) = 18.0 + 14.3 + 28.0 + 15.3 + 15.6 = **91.2 / 100 [VERY HIGH]**

95% CI: [87.4, 94.1]

PSP (Standard Tier):

- Sorafenib signal: (82×0.50) + (100×0.30) + (100×0.20) = 41+30+20 = **91.0 [VERY HIGH]**
- Lenvatinib signal: (82×0.60) + (100×0.25) + (100×0.15) = 49.2+25+15 = **89.2 [VERY HIGH]**
- Atezo/Bev signal: (82×0.55) + ((100-85)×0.45) = 45.1+6.75 = **51.9 [HIGH]**

Interpretive note: This profile is characterised by very high angiogenic burden, macrovascular invasion, and elevated NLR. The high NLR (score=85) substantially penalises the Atezo/Bev immune proxy in Standard Tier — the inverted NLR signal (100-85=15) reflects a systemic inflammatory milieu generally associated with attenuated immune activity. Both anti-angiogenic pathway signals (sorafenib and lenvatinib) are very high. Without FGFR data, the framework cannot differentiate between them on angiogenic grounds alone. Extended Tier profiling — particularly FGFR amplification status — would be the most informative next step to distinguish lenvatinib-specific from sorafenib-consistent signals in this profile. This analysis does not recommend either agent over the other.

Scenario 3 — Extended Tier: Immune-Inflamed Profile with FGFR Signal

Source: Representative of an immune-activated HCC profile. The Atezo/Bev arm of [Finn et al., IMbrave150, NEJM, 2020] enrolled patients without macrovascular invasion of the main portal vein or biliary invasion; the responder subgroup in that trial tended to have lower NLR and evidence of immune activation. This scenario is consistent with the described characteristics of the immune-enriched subgroup. TME values (PD-L1 TPS, TIL density) are representative of the PD-L1-positive (≥1%) subgroup reported in IMbrave150 exploratory analyses.

Profile (Extended Tier): AFP 310 ng/mL, AFP-L3 9%, DCP 88 mAU/mL, MVI M1 (2 foci), NLR 2.3, VEGF 195 pg/mL. Extended: 2 CTCs detected/7.5 mL, ctDNA VAF 1.8%, E-cadherin reduced (positive), vimentin negative, CTNNB1 wildtype, PD-L1 TPS 12%, TIL-high, FGFR2 amplification detected, TP53 wildtype, PTEN intact, RB1 intact, epigenetic dysregulation: not reported.

Standard Tier subscores:

- AFP: AFP=310 → between (200, score=50) and (400, score=75) → score = 50 + (310-200)×25/200 = **63.8**; AFP-L3=9% (<15%) → no add-on → **63.8**
- DCP: DCP=88 → between (85, score=55) and (400, score=80) → score = 55 + (88-85)×25/315 = **55.2**
- MVI: M1 → **50**
- NLR: NLR=2.3 → between (2.0, score=0) and (2.5, score=15) → score = 0 + (2.3-2.0)×15/0.5 = **9.0**
- VEGF: VEGF=195 → between (150, score=25) and (250, score=55) → score = 25 + (195-150)×30/100 = **38.5**

Extended Tier additional subscores:

- CTC/ctDNA: 2 CTCs, VAF 1.8% → CTC: 25 (1–2 CTCs); VAF 0.5–2% category → combined estimated: **40**
- TME: PD-L1 TPS 12% (≥10% → +50); TIL-high (+30); NLR 2.3 (<5 → no penalty) → score = **80**
- EMT: E-cadherin loss (+35); vimentin negative (0); CTNNB1 wildtype (0) → **35**
- FGFR: FGFR2 amplification → **85**
- Genetic: TP53 wildtype, PTEN intact, RB1 intact → **0**

Composite (Extended Tier, all 10 domains): = (63.8×0.11) + (55.2×0.11) + (50×0.17) + (9.0×0.11) + (38.5×0.11) + (40×0.10) + (80×0.10) + (35×0.07) + (85×0.03) + (0×0.09) = 7.0 + 6.1 + 8.5 + 0.99 + 4.24 + 4.0 + 8.0 + 2.45 + 2.55 + 0 = **43.8 / 100 [HIGH]**

95% CI: [40.2, 47.5]

PSP (Extended Tier):

- Sorafenib signal: (38.5×0.50) + (63.8×0.30) + (50×0.20) = 19.25+19.14+10 = **48.4 [HIGH]**

- Lenvatinib signal: (38.5×0.40) + (85×0.30) + (63.8×0.20) + (50×0.10) = 15.4+25.5+12.76+5 = **58.7 [HIGH]**
- Atezo/Bev signal: (80×0.55) + (38.5×0.30) + (40×0.15) = 44+11.55+6 = **61.6 [VERY HIGH]**

Interpretive note: This profile illustrates the value of Extended Tier data. In Standard Tier alone, the moderate angiogenic and MVI signals produce comparable sorafenib and lenvatinib signals. The Extended Tier adds two important differentiating signals: (1) FGFR2 amplification elevates the lenvatinib-specific pathway signal above sorafenib — reflecting lenvatinib's unique capacity to block FGFR-driven angiogenic escape [Shitara et al. 2024]; and (2) the high PD-L1 TPS + TIL-high TME, combined with low NLR and CTNNB1 wildtype status (consistent with an immune-inflamed phenotype [Ruiz de Galarreta et al. 2019]), drives a very high Atezo/Bev signal. These are research-level pathway hypotheses — the overlap between lenvatinib and Atezo/Bev signals here reflects the emerging interest in lenvatinib + checkpoint inhibitor combinations for immune-active, FGFR-amplified HCC. Neither agent is recommended nor excluded by this output.

---

9. References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. DOI: 10.3322/caac.21660

2. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *New England Journal of Medicine*. 2008;359(4):378–390. DOI: 10.1056/NEJMoa0708857

3. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial (REFLECT). *Lancet*. 2018;391(10126):1163–1173. DOI: 10.1016/S0140-6736(18)30207-1

4. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma (IMbrave150). *New England Journal of Medicine*. 2020;382(20):1894–1905. DOI: 10.1056/NEJMoa1915745

5. Lok AS, Sterling RK, Everhart JE, et al. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of HCC. *Gastroenterology*. 2010;138(2):493–502. DOI: 10.1053/j.gastro.2009.10.031

6. Mendez-Blanco C, et al. Prognostic value of a simplified score based on routine parameters in patients with HCC treated with systemic therapies. *PMC (in press)*. 2024.

7. Ou Q-J, et al. Neutrophil-to-lymphocyte ratio for the prognostic assessment of HCC: a systematic review and meta-analysis of observational studies (90 studies, 20,475 patients). *Oncotarget*. 2016.

DOI: 10.18632/oncotarget.10030

8. Cai W, et al. Prognostic value of VEGF in HCC patients treated with sorafenib: a meta-analysis (9 studies). *Medical Science Monitor*. 2015. PMC: PMC4617189.

9. Xie H, et al. MRI-based intra- and peritumoral heterogeneity in HCC for MVI prediction and prognostic risk stratification (OS HR 2.68; recurrence HR 2.17). *Radiology: Imaging Cancer*. 2025.

10. Shirabe K, et al. Microvascular invasion in patients with HCC and its predictable clinicopathological factors (5-yr OS: 59.3% vs 92.0% with/without MVI). *Hepatology Research*. 2008. DOI: 10.1111/j.1872-034X.2008.00330.x

11. Ribero D, et al. Scoring microvascular invasion in hepatocellular carcinoma: are we meeting the grade? (M0/M1/M2 5-yr OS data). *PMC / Hepatobiliary Surgery and Nutrition*. 2024. PMC: PMC10839732.

12. Swenerton R, et al. AFP-L3 and DCP strongly predict early HCC recurrence after liver transplantation (prospective cohort, n=285). *PMC*. 2024. PMC: PMC10998694.

13. Hamzah N, Kassim NK, Omar J, et al. Levels of PIVKA-II and AFP in unresectable HCC: median PIVKA-II 988.4 vs. 24.2 mAU/mL in controls. *PeerJ*. 2023. DOI: 10.7717/peerj.15988

14. Imamura H, et al. Risk factors contributing to early and late phase intrahepatic recurrence of HCC after hepatectomy. *Journal of Hepatology*. 2003;38(2):200–207. DOI: 10.1016/S0168-8278(02)00360-4

15. Ren T, Hou X, Zhang X, et al. Validation of combined AFP, AFP-L3, and PIVKA-II for diagnosis and monitoring of HCC in Chinese patients. *Heliyon*. 2023;9(11):e21906. DOI: 10.1016/j.heliyon.2023.e21906

16. Wang H, et al. Importance of MVI risk and tumor size on recurrence and survival of HCC after anatomical and non-anatomical resection (NLR >3.8 associated with MVI; AUROC 0.884). *Frontiers in Oncology*. 2021. DOI: 10.3389/fonc.2021.621622

17. Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nature Reviews Clinical Oncology*. 2022;19(3):151–172. DOI: 10.1038/s41571-021-00573-2

18. Ruiz de Galarreta M, Bresnahan E, Molina-Sánchez P, et al. β-catenin activation promotes immune evasion and resistance to anti-PD-1 therapy in HCC. *Cancer Discovery*. 2019;9(8):1124–1141. DOI: 10.1158/2159-8290.CD-19-0074

19. Schulze K, Imbeaud S, Letouzé E, et al. Exome sequencing of HCC identifies new mutational signatures and potential therapeutic targets. *Nature Genetics*. 2015;47(5):505–511. DOI:

10.1038/ng.3252

20. Ye Q, Ling S, Zheng S, Xu X. Liquid biopsy in HCC: circulating tumor cells and circulating tumor DNA. *Molecular Cancer*. 2019;18(1):114. DOI: 10.1186/s12943-019-1043-x

21. Ikeda M, et al. Pharmacodynamic biomarkers predictive of survival benefit with lenvatinib in unresectable HCC: from the phase III REFLECT study (FGF21 as predictive for lenvatinib OS benefit). *Clinical Cancer Research*. 2021. DOI: 10.1158/1078-0432.CCR-20-4754

22. Shitara K, et al. Lenvatinib and immune-checkpoint inhibitors in HCC: mechanistic insights, clinical efficacy, and future perspectives (FGFR vs. VEGFR pathway differentiation). *PMC*. 2024. PMC: PMC11663365.

23. Hoshida Y, Villanueva A, Kobayashi M, et al. Gene expression in fixed tissues and outcome in HCC. *New England Journal of Medicine*. 2008;359(19):1995–2004. DOI: 10.1056/NEJMoa0804525

24. Ma L, Wang L, Khatib SA, et al. Single-cell atlas of tumor cell evolution in response to treatment in HCC and intrahepatic cholangiocarcinoma (LNMAHs and PVMAHs). *Journal of Hepatology*. 2021;75(6):1397–1408. DOI: 10.1016/j.jhep.2021.06.028

25. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology*. 2018;69(1):182–236. DOI: 10.1016/j.jhep.2018.03.019

HCC-METASCORE v2 is a research framework for structured biomarker reasoning. Weights are derived from published hazard ratios; transformation functions are anchored to published clinical thresholds. The tool has not been prospectively calibrated or externally validated. It is not a medical device and not for use without expert clinical oversight.