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Review Article

Milestones in Hepatocellular Carcinoma (HCC) Research – Worldwide

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Abstract

In recent years, Austrian researchers have made substantial contributions to the field of hepatocellular carcinoma (HCC). Notably, novel prognostic markers and risk-stratification tools have been developed for systemic immunotherapy, transarterial chemoembolization (TACE), and liver transplantation. In particular, the CRAFITY score, sarcopenia, and dynamic IgG changes significantly refine prognostic assessment under immunotherapy. For intermediate-stage disease, the STATE, ART, and START scores enable increasingly individualized decisions regarding TACE suitability. A possible advancement in transplant selection is the AFP-UTS model, which integrates morphological tumor characteristics from the Up-to-seven criteria combined with AFP levels, allowing reliable discrimination between patients with favorable tumor biology and those at high risk of post-transplant recurrence. Additionally, the efficacy and safety of systemic first- and second-line therapies have been externally validated through large multicenter real-world cohorts involving Austrian centers. This applies particularly to heterogeneous patient populations and includes Sorafenib, Lenvatinib, Cabozantinib, and the Atezolizumab–Bevacizumab combination, now established as the standard first-line immunotherapy for advanced HCC.

Keywords: Hepatocellular carcinoma (HCC); Prognostic Markers; Immunotherapy; Transarterial Chemoembolization (TACE); Liver transplantation;

CRAFITY score – prognosis under immunotherapeutic treatment

The CRAFITY score (CRP and AFP in Immunotherapy) was developed in a European HCC cohort of patients treated with immunotherapy (PD-(L)1 inhibitors). In the analysis, AFP ≥ 100 ng/ml and CRP ≥ 1 mg/dl were identified as independent predictors of overall survival. Each factor was assigned one point, resulting in three risk groups (0/1/2 points). The applicability of the score was consistent in both Child-Pugh A and Child-Pugh B patients. Median overall survival was 27.6, 11.3, and 6.4 months for scores 0–2, respectively ($p < 0.001$). Analogously, a high CRAFITY score was associated with a poorer radiological response rate: in the validation cohort, tumor response according to mRECIST correlated significantly with the score. Higher scores were therefore associated with increased rates of disease progression. Notably, while the score also predicted survival in a comparison cohort receiving standard therapy (sorafenib), no correlation with tumor response was observed—highlighting the score's specific prognostic value under immunotherapy. The CRAFITY score was validated in multiple cohorts (1). Since then, it has been internationally adopted as a tool for estimating prognosis under PD-(L)1 checkpoint inhibition [1-3].

Additional prognostic markers under immunotherapy: sarcopenia and IgG increase

Additional negative prognostic factors under immunotherapy include sarcopenia and a dynamic increase in immunoglobulin G [4, 5]. In a multicenter study (Paris, Vienna), sarcopenia was assessed using transversely measured psoas muscle thickness (TPMT). Approximately one third of patients (33%) already had sarcopenia before treatment initiation. Sarcopenia was associated with a median overall survival of 7.2 months compared with 22.6 months in patients without sarcopenia ($p < 0.001$), as well as with inferior progression-free survival (3.4 vs. 7.9 months; $p = 0.001$) and a lower objective response rate 22% vs. 39%; $p \approx 0.03$) [4]. These findings partially align with results from the Austrian-led INSIGHT registry, which demonstrated markedly reduced survival under sorafenib in patients with impaired fitness (Child B) (median approximately 8 months vs. ~18 months in Child A) [6]. In a Viennese study, serum IgG levels were measured six weeks before and after initiation of immune checkpoint inhibitor (ICI) therapy. A pronounced increase in total IgG (ΔIgG ≥ +14%) was independently associated with shorter survival (6.4 vs. 15.9 months; $p = 0.001$). Baseline IgG levels showed no prognostic relevance; rather, the prognostic value lay in their dynamics. IgG increase remained an independent prognostic factor in multivariable analysis, whereas IgA and IgM showed no association with survival. An excessive IgG increase may reflect dysregulated immune activation or subclinical infections during immunotherapy [5].

Suitability for TACE – STATE and ART/START scores

Hucke et al. developed the STATE and ART/START scores as key instruments for selecting suitable TACE candidates [7-9]. The STATE score (Selection for TrAnsarterial chemoembolisation TrEatment) stratifies patients based on albumin, tumor burden, and CRP into two groups (< 18 vs. ≥ 18 points). Patients with a low STATE score (< 18) achieved a median overall survival of 5.3 months, whereas those with a high STATE score (≥ 18) survived 19.5 months ($p < 0.001$). Early TACE failure occurred more frequently in patients with a low STATE score (39% vs. 14%), as did increased 30-day mortality after first TACE [7].

The ART score (Assessment for Retreatment with TACE) identifies patients who benefit from repeat TACE and incorporates an AST increase > 25%, worsening of the Child-Pugh score by ≥ 1 point, and absence of tumor response. Patients with a low ART score (< 1.5) achieved a median OS of 23.7 months, whereas scores ≥ 2.5 were associated with only 6.6 months ($p < 0.001$). High ART scores were additionally associated with increased rates of hepatic decompensation and lack of survival benefit [8, 9]. The START score (Selection for TACE Retreatment) was developed as an alternative to the ART score and includes albumin < 3.5 g/dl, bilirubin > 1.5 mg/dl, pre-interventional AST > 100 U/l, and absence of objective tumor response at 6–8 weeks (mRECIST). With 0–1 points, median survival was 23.3 months, whereas with ≥ 3 points it was 6.8 months ($p < 0.001$) [7]. These models demonstrate that not all BCLC B patients benefit from TACE and shift the focus from a purely stage-based treatment decision toward individualized patient selection. Selective use of TACE in unsuitable patients (e.g., those with advanced tumor burden or impaired liver function) can reduce treatment-associated harm and thereby improve prognosis in high-risk patients [7-9].

Systemic Therapy

The development of systemic therapy for HCC in recent years has been substantially shaped by international phase III trials. Austrian centers have contributed important validation data primarily through multicenter real-world analyses, particularly regarding first- and second-line therapies with sorafenib, lenvatinib, cabozantinib, and atezolizumab + bevacizumab, thereby confirming the transferability of clinical trial results into routine clinical practice [6, 10-12]. One of the earliest and most comprehensive studies was the INSIGHT study, which evaluated the efficacy and safety of sorafenib as systemic first-line therapy [6]. The results confirmed the median overall survival observed in the SHARP trial in a real-world setting. The patient distribution differed markedly from the population-selected SHARP study: in INSIGHT, 7% of patients were classified as BCLC A, 29% as BCLC B, 57% as BCLC C, and 7% as BCLC D, whereas SHARP exclusively included BCLC C patients with preserved liver function (Child-Pugh A). Thus, INSIGHT represented a more heterogeneous cohort that also included earlier tumor stages. The median overall survival for the entire cohort was 15.1 months with clear differences between stages (29.2 months in BCLC A, 19.6 months in BCLC B, 13.6 months in BCLC C, 3.1 months in BCLC D). These values were overall higher than those reported in the SHARP study (10.7 months vs. 7.9 months under placebo), which was attributed to better liver function and earlier tumor stages in INSIGHT. Median time to progression was 4.8 months, comparable to SHARP (5.5 months) [6, 13]. Prior to EMA approval of the tyrosine kinase inhibitors (TKIs) regorafenib (2017) and cabozantinib (2018), as well as the VEGF inhibitor ramucirumab (2019), no approved second-line therapies were available [10, 14, 15]. In the early 2010s, PD-1 inhibitors (nivolumab, pembrolizumab) were therefore used as de facto second-line therapies within clinical trials. This is clearly reflected in the study populations of CheckMate-040 and KEYNOTE-224 [16, 17]. In this context, an international real-world cohort study with Austrian participation provided important data on nivolumab and pembrolizumab [18]. Both agents were used as second-line therapy in HCC patients with radiological progression or significant sorafenib-associated toxicity [16, 17]. Median OS was 11 months;

stratified by Child-Pugh class, median OS was 16.7 months in Child-Pugh A and 8.6 months in Child-Pugh B patients [18]. These values were slightly below the reference data from early immunotherapy trials: nivolumab achieved a median OS of 15.1 months in CheckMate-040, while pembrolizumab reached 13.2 months in KEYNOTE-224/240 [16, 17, 19]. Despite promising activity, no EMA approval was granted, as both CheckMate-459 (nivolumab vs. sorafenib) and KEYNOTE-240 (pembrolizumab vs. placebo) narrowly missed their primary endpoints [17, 20]. PD-1 blockade thus represents a therapeutic transitional phase of the pre-TKI era. In parallel, real-world analyses with Austrian participation confirmed the effectiveness of the newly approved TKIs. The analysis by Scheiner et al. demonstrated a median OS under cabozantinib of 7.0 months overall, 9.7 months in Child-Pugh A, and 3.4 months in Child-Pugh B patients [10]. In the CELESTIAL-conform subgroup, OS was 11.1 months, nearly identical to CELESTIAL (10.2 months) [21]. Under lenvatinib, the ELEVATOR study reported a median OS of 12.8 months; REFLECT-conform patients achieved 15.6 months, thereby even exceeding the values observed in the REFLECT trial (13.6 months) [11, 22]. These data underscore that patients with well-preserved liver function derive the greatest benefit from systemic therapy [10, 23, 24]. In the international IMbrave150 study comparing atezolizumab + bevacizumab with sorafenib, the combination demonstrated a significant overall survival and progression-free survival benefit over sorafenib and was established as a first-line standard in 2020 (EMA approval) [25-27]. A multicenter real-world analysis from four centers in Germany, Austria, and Switzerland evaluated the effectiveness and tolerability of this combination in routine clinical practice and, in contrast to IMbrave150, also included patients with more impaired liver function (Child-Pugh A 52%, B 35%, C 8%) [18]. Although median OS had not been reached at the time of analysis, robust 12- and 18-month survival rates were observed [12]. Compared with the IMbrave150 trial, PFS (6.5 vs. 6.8 months) and objective response rate (29% vs. 27.3%) were nearly identical, whereas 12-month OS (60% vs. 67.2%) and 18-month OS (52% vs. 58%) were slightly lower. The higher bleeding rate (30% vs. 7%) was explained by the inclusion of patients with more advanced cirrhosis. A subgroup analysis showed that patients with viral hepatitis achieved a significantly longer PFS (17.3 vs. 6.1 months; HR 0.48) compared with non-viral cases. These data confirm the effectiveness of atezolizumab + bevacizumab in routine clinical practice, but also emphasize the importance of careful patient selection and demonstrate that patients with Child-Pugh A cirrhosis benefit most, whereas use in Child-Pugh B/C should only be considered after strict risk–benefit assessment [12, 25, 26].

In the phase III HIMALAYA study, the STRIDE regimen with tremelimumab + durvalumab was implemented as an alternative first-line therapy to atezolizumab + bevacizumab. STRIDE demonstrated a significant OS benefit compared with sorafenib (median OS 16.43 vs. 13.77 months) [28]. The objective response rate was 20.1%, lower than in the IMbrave study (27.3%) [27, 28]. Although the patient cohorts in IMbrave and HIMALAYA both consisted of 100% Child-Pugh A patients, substantial differences in baseline characteristics were observed. In comparison of the study populations, IMbrave150 was prognostically more unfavorable than HIMALAYA (macrovascular invasion 38% vs. 26.2%, extrahepatic metastasis 63% vs. 53.2%, and inclusion vs. exclusion of main portal vein thrombosis) [27-29]. For practical regimen selection, it is relevant that IMbrave150, due to VEGF blockade (bevacizumab), required standardized variceal screening in the protocol and excluded patients at high bleeding risk, rendering STRIDE more frequently discussed as an option in patients with increased variceal bleeding risk [30]. Conversely, based on available data from IMbrave and HIMALAYA, it can be inferred that atezolizumab + bevacizumab should be preferred over the STRIDE regimen in patients with higher tumor burden (higher response rate, higher median OS, and greater survival benefit despite worse tumor characteristics) [27, 28].

Summary: 17 years of systemic therapy-from sorafenib (2006) to atezolizumab + bevacizumab (2020) and tremelimumab + durvalumab (2022)

Before the introduction of systemic therapies, median survival in the palliative setting was usually below 8 months. With sorafenib, a significant survival benefit was achieved for the first time (10.7 vs. 7.9 months in SHARP) [13]. Subsequently, regorafenib, cabozantinib, and ramucirumab achieved median overall survival times of 8.5–10.6 months in the second-line setting, with absolute survival gains of approximately 1.2–2.8 months compared with placebo [14, 15, 21].

The greatest advance, however, was marked by IMbrave150, in which atezolizumab + bevacizumab achieved a median OS of approximately 19 months and a 12-month survival rate of 67%. In addition, combination therapy reported a complete response under systemic therapy for the first time in a BCLC C stage [26, 27]. As a further first-line option, tremelimumab + durvalumab represents an alternative for patients with inoperable HCC and a high bleeding risk due to esophageal varices.

Liver transplantation: AFP-adjusted-to-HCC-size (AFP-UTS) criteria

The Viennese working group led by Meischl et al. (2021) developed the AFP-UTS criteria as an extension of the morphological up-to-seven model by incorporating a biological marker (AFP ≤ 1000 ng/ml) in order to selectively exclude patients with aggressive tumor biology within the UTS group. Under AFP-UTS, patients achieved excellent long-term outcomes: median OS was approximately 127 months, the 5-year survival rate exceeded 70%, and the

5-year recurrence rate was only 18%. When AFP-UTS criteria were exceeded, outcomes deteriorated markedly: median OS approximately 34 months, 5-year survival approximately 43%, and a recurrence rate of 64%. Early recurrence (< 24 months) proved to be the strongest driver of mortality, with a median OS of only approximately 17 months compared with approximately 122 months in the absence of early recurrence [31]. In comparison, the Milan criteria (single lesion ≤ 5 cm or up to three lesions ≤ 3 cm) achieved a 5-year survival rate of 73.3% in the original publication and only 8% recurrence after 4 years [32, 33]. The up-to-seven criteria later expanded the indication morphologically and achieved comparable 5-year survival rates of 71.2%. However, patients within the up-to-seven criteria exhibited a substantially lower recurrence-free 5-year survival compared with the Milan criteria (86.2% vs. 76.6%). Indicates an increased recurrence rate within the UTS criteria [34, 35]. It thus became evident that purely morphological models cannot adequately capture a biologically high-risk subgroup [36]. By combining morphology and AFP, AFP-UTS criteria systematically address this gap. In direct comparison, a nearly equal number of patients are newly included or excluded by AFP-UTS: in the original Viennese cohort, 127 of 166 patients (77%) fulfilled both Milan and AFP-UTS criteria, whereas 12 Milan-in patients were excluded due to AFP > 1000 ng/ml, and at the same time 12 Milan-out patients (UTS-in with low AFP) were newly included. The net effect is therefore less an expansion of the overall cohort than a redistribution: biologically unfavorable but morphologically favorable cases are excluded, while biologically favorable but morphologically extended cases are included [31]. This dynamic may explain why long-term overall survival rates between Milan, UTS, and AFP-UTS remain similar at the population level, despite clearly divergent recurrence risks. The exchange between Milan-in patients with poor prognosis (high AFP) and Milan-out patients with favorable tumor biology (low AFP) appears to neutralize itself in the overall cohort. At the same time, AFP-UTS enables a selected subgroup beyond the Milan limits—biologically favorable Milan-out patients—to access curative-intent transplantation with excellent long-term outcomes, comparable to the Milan criteria. In summary, Milan remains a robust baseline model with a slightly superior 5-year survival rate (73.3% vs. 71.2%) and very low recurrence rates (8–15%) [32, 34]. Up-to-seven expands the indication morphologically but is associated with significantly higher recurrence rates [34]. Criteria combining tumor burden and AFP currently represent the most precise integration of tumor morphology and tumor biology, as they enable early identification of biologically aggressive tumors while allowing a safe and controlled expansion beyond the classical Milan criteria. The clinical net effect therefore lies less in an expansion of the overall cohort than in targeted optimization of patient selection and improved transplant safety [31].

Summary

Austrian research groups have provided key advances in prognostic evaluation and therapeutic optimization of HCC. Under immunotherapy, the CRAFITY score identifies clear prognostic strata (OS 27.6 vs. 11.3 vs. 6.4 months). Sarcopenia decreases median survival from 22.6 to 7.2 months, while a dynamic IgG increase (≥14%) halves median OS from 15.9 to 6.4 months. For TACE selection, the STATE, ART, and START scores demonstrate substantial outcome separation (STATE cutoff: 5.3 vs. 19.5 months mOS [<18 vs. ≥18 points]; ART: 6.6 vs. 23.7 months mOS [≥2.5 vs. <1.5 points]; START: 6.8 vs. 23.3 months mOS [≥3 vs. 0–1 points]). Systemic therapies have been confirmed in real-world settings: Sorafenib achieved 29.2–13.6 months OS across BCLC A–C, while Cabozantinib and Lenvatinib reached up to 11.1 and 15.6 months mOS. Atezolizumab plus Bevacizumab achieved 12-month OS rates of 60%. The AFP-UTS transplant selection model enables exceptional post-transplant outcomes with ~127 months OS, >70% 5-year survival, and only 18% recurrence.

Conflict of Interest: The authors declare that they have no conflict of interest.

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