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Hepatocellular Carcinoma in Practice: Should I Bev or should IO?

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Hepatocellular carcinoma in practice: should I Bev or should IO?

Angiogenesis plays an important role in the development and metastasis of hepatocellular carcinoma (HCC), and is strongly stimulated by hypoxia [1,2]. Hypoxia-inducible factor-1α (HIF-1α), the main transcription factor activated by hypoxia, triggers the expression of a range of target genes including vascular endothelial growth factors (VEGFs), platelet-derived growth factors (PDGFs), fibroblast growth factors (FGFs), and angiopoietins, which contribute to cell survival and angiogenesis under hypoxic conditions [3,4].

Additionally, the unique vascularization of the liver—supplied by two afferent circulations (portal vein and hepatic artery)—highlights the critical importance of angiogenesis in HCC. This anatomical peculiarity laid the foundation for the development of antiangiogenic therapies, both in early/intermediate and advanced stages of the disease [5].

Antiangiogenic drugs have been the cornerstone of advanced HCC treatment since 2007 [6-9]. However, despite improvements in clinical outcomes with targeted therapies, median overall survival (OS) remains poor.

First-line treatment options recommended by leading international guidelines include immuno-oncology (IO) with a combination of checkpoint inhibitors and anti-CTLA-4, and IO drugs combined with antiangiogenic agents [10-12]. Although the incorporation of IO drugs has significantly advanced outcomes in advanced HCC [13,14], there are still no established biomarkers to guide the optimal choice of systemic therapy. Antiangiogenic agents remain essential in achieving better oncological outcomes, whether in the advanced or intermediate disease setting (Table 1).

The pivotal phase 3 IMbrave150 trial, which evaluated patients with unresectable HCC who had not received prior systemic treatment, showed that the combination of atezolizumab and bevacizumab resulted in better median OS (19.2 months vs. 13.4 months; hazard ratio [HR] 0.66; 95% CI 0.52–0.85; $p < 0.001$) and median progression-free survival (PFS) (6.9 vs. 4.3 months; HR 0.65; 95% CI 0.53–0.81; $p < 0.001$) compared to sorafenib [15]. This benefit was evident early, with survival curves separating within the first few months and remaining consistently apart throughout the study follow-up—indicating strong statistical robustness. Notably, in the combination therapy arm, 19% of patients had high-risk characteristics, such as portal vein tumor thrombosis (Vp4), involvement of more than 50% of the liver, or bile duct invasion [15].

A systematic review and meta-analysis of 2,179 patients from 12 real-world cohorts confirmed the long-term efficacy of atezolizumab plus bevacizumab for unresectable HCC, with a median OS of 20.9 months (95% CI: 15.7–20.9)—consistent with clinical trial outcomes. At 24 months, the median OS was 39% (95% CI: 31–49; $I^2 = 90\%$) and the median PFS was 25% (95% CI: 12–45; $I^2 = 95\%$) [14]. The AB combination also achieved a high disease control rate (DCR) of 74%, including 30% objective response rate (ORR) and 8% complete response (CR). Only 19% of patients had disease progression as their best response [16]. These data support AB as an excellent option, even for high-risk patients, and with potential for downstaging.

In the intermediate disease setting, prospective data—although still immature for OS—also suggest a key role for antiangiogenic

Table 1: Phase III superiority trials evaluating antiangiogenic therapy in intermediate and advanced HCC.

Study	Treatment	N	ORR	PFS	OS	p; HR (95% CI)	G3/4 AE
LEAP-012 [17]	TACE + Lenvatinib + Pembro TACE + placebo	237 243	46.8% 33.3%	14.6m 10m	- -	.0002; 0.66 (0.51 - 0.84)	71.3% 31.1%
EMERALD-1 [18]	TACE + Durva TACE + Durva + Bev TACE + placebo	207 204 205	41% 43.6% 29.6%	10m 15m 8.2m	- - -	0.64; 0.94 0.032; 0.77 (0.61 - 0.98)	27.6% 45.5% 23%
IMBRAVE-15 [15]	Atezolizumab + Bev Sorafenib	336 165	27.3% 11.9%	6.9m 4.3m	19.2m 13.4m	<0.001; 0.66 (0.52 - 0.85)	56.5% 55.1%
CARES-310 [19]	Camrelizumab + Rivoceranib Sorafenib	272 271	24.5% 5.9%	5.6m 3.7m	22.1m 15.2m	<.0001; 0.62 (0.49 - 0.80)	81% 52%
APOLLO [20]	Panpulimab + Anlotinib Sorafenib	433 216	21% 7%	6.9m 2.8m	16.5m 13.2m	0.014; 0.69 (0.55 - 0.87)	50% 48%
ORIENT-32 [21]	Sintilimab + Bev Sorafenib	380 191	21% 4%	4.6m 2.8m	NR 10.4m	<0.001; 0.57 (0·43–0·75)	53% 45%

N: number; ORR: objective response rate; PFS: progression-free survival; OS overall survival; HR: hazard ratio; CI: confidence interval; G: grade; AE: adverse events; TACE: transarterial chemoembolization; Pembro: pembrolizumab; Durva: durvalumab; Bev: bevacizumab.

therapy in improving disease-free survival when combined with transarterial chemoembolization (TACE) [17,18].

The phase III superiority trials LEAP-012 and EMERALD-1 showed PFS gains for TACE + Lenvatinib + Pembrolizumab vs. TACE + placebo (14.6 vs 10 months; HR 0.66 (95% CI: 0.51–0.84); p = 0.0002); and TACE + Durvalumab + Bevacizumab vs. TACE + placebo (15 vs 8.2 months; HR 0.77 (95% CI: 0.61–0.98); p = 0.032) [17,18]. However, Durvalumab without bevacizumab did not show superiority over placebo when combined with TACE (10 vs 8.2 months; HR 0.94; 95% CI: 0.75–1.19; p = 0.64) in EMERALD-1 trial [18].

There are ongoing concerns regarding toxicity, particularly bleeding and thromboembolic events, when using antiangiogenic therapies in patients with cardiovascular comorbidities or cirrhosis. Nevertheless, there is no formal contraindication to the use of bevacizumab in the presence of portal hypertension [22,23].

In the IMbrave150 trial, grade 3–4 bleeding events occurred in approximately 6.4% of patients treated with atezolizumab plus bevacizumab compared with 5.8% in the sorafenib group; most bleeding episodes were grade 1–2. The risk of variceal or gastrointestinal bleeding was higher among patients with baseline varices or Vp4 portal vein invasion, which justified the protocol requirement for endoscopy within six months prior to treatment initiation. Exploratory and observational data indicate arterial thromboembolic events in roughly 2–3% of patients receiving atezolizumab–bevacizumab versus about 1% with sorafenib [15]. Despite a modest increase in bleeding and thrombotic risk, atezolizumab plus bevacizumab was associated with delayed deterioration in health-related quality of life compared with sorafenib and transarterial radioembolization [24].

The consistency of benefits across studies, the ability to improve survival in both advanced and intermediate disease settings, and the fact that they target a pathway central to HCC development and metastasis, make antiangiogenic agents a key consideration in the systemic treatment decision-making process for HCC patients. It can be administered safely in patients with hepatic impairment, provided that bleeding risk is carefully evaluated and managed within a multidisciplinary liver tumor team and in adequately equipped healthcare settings.

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