Editorial Commentary

Tislelizumab: a promising alternative first-line systemic therapy in unresectable advanced hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) poses a significant clinical challenge globally, with limited treatment options, particularly for patients with advanced and unresectable disease, and additional systemic treatment options are required to enhance outcomes and treatment tolerability. Recent advancements in immunotherapy have opened new avenues for treatment, challenging the standard of care dominated by the multikinase inhibitor schedules. In 2020, the European Medicines Agency (EMA) approved, as first-line, the combination therapy of atezolizumab [anti-programmed death ligand-1 (anti-PD-L1)] plus bevacizumab [anti-vascular endothelial growth factor (anti-VEGF)] (1) and in February 2023 (in Europe) durvalumab (anti-PD-L1) plus tremelimumab [anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4)] (2) as an alternative strategy in the landscape of first-line therapy.

In this scenario, the most recent new entry is tislelizumab (anti-programmed death receptor-1, PD-1-inhibitor), evaluated in the RATIONALE-301 trial, conducted by Finn *et al.* (3). The study's findings presented compelling insights into the efficacy and safety of tislelizumab in this setting.

Tislelizumab is a humanized monoclonal antibody targeting PD-1 and its role in the field of immunotherapy is of growing interest. Up to now, it has been approved by EMA as a second-line therapy in unresectable or metastatic esophageal squamous cell carcinoma (4), and in February 2024 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) (5).

Since a few years ago, Tislelizumab has shown potential as an option in the landscape of systemic therapies for HCC. Indeed, promising outcomes emerged from a previous phase 2 trial (RATIONALE-208), in which it was evaluated in advanced HCC progression to first-line therapies. The trial demonstrated a durable objective response rate (ORR) of 13% in a median of 12.7 months, irrespective of the number of prior lines of therapy, along with a disease control rate of 53%, with an acceptable tolerability (6).

The phase 3 randomized clinical trial RATIONALE-301 (3) compared tislelizumab with sorafenib as first-line treatment for unresectable HCC and after 36-month of follow-up, tislelizumab resulted from non-inferior to sorafenib.

The results of the trial demonstrate similar overall survival (OS) [15.9 months, 95% confidence interval (CI): 13.2–19.7 *vs.* 14.1 months, 95% CI: 12.6–17.4] and improved progression-free survival (PFS) (2.1 months, 95% CI: 2.1–3.5 *vs.* 3.4 months, 95% CI: 2.2–4.1) compared to sorafenib. Responses were more frequent (ORR: 14.3% *vs.* 5.4%) and durable (36.1 *vs.* 11.0 months) in the tislelizumab arm compared to sorafenib, indicating its potential for inducing more robust antitumor responses.

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Table 1 Cross-trial comparison: differences between goals of treatment of the first-line immunotherapy regimens for treatment of HCC, both study arms, including sorafenib arms, are shown

Cross-trial comparison	ORR (95% CI), %		OS (95% CI), months		PFS (95% CI), months		Main inclusion/exclusion criteria
	Experimental therapy	Sorafenib	Experimental therapy	Sorafenib	Experimental therapy	Sorafenib	
IMBRAVE-150 (1), atezolizumab-bevacizumab	27.3 (22.5–32.5)	11.9 (7.4–18.0)	19.2 (17.0–23.7)	13.4 (11.4–16.9)	6.9 (5.7–8.6)	4.3 (4.0–5.6)	Inclusion: unresectable HCC, BCLC B or C, Child Pugh A, no previous sistemic therapy Exclusion: autoimmune disease, coinfection HBV/HCV, untreated or incompletely treated varices with bleeding or high risk of bleeding
HIMALAYA (2), durvalumab-tremelimumab	20.1 (16.2–24.4)	5.1 (3.1–7.8)	16.4 (14.1–19.5)	13.7 (12.2–16.1)	3.7 (3.6–5.3)	4.1 (3.7–5.5)	Inclusion: histologically confirmed HCC, unresectable HCC, BCLC B or C, Child Pugh A, no previous sistemic therapy Exclusion: meaningful ascites, main PVT
CARES-310 (11), camrelizumab-rivoceranib	25.3 (20.3–30.9)	5.9 (3.4–9.4)	22.1 (19.1–27.2)	15.2 (13.0–18.5)	5.6 (5.5–6.3)	3.7 (2.8–3.7)	Inclusion: histo-/cytologically confirmed HCC, unresectable HCC, BCLC B or C, Child Pugh A, no previous sistemic therapy Exclusion: history of high risk of gastrointestinal bleeding, hypertension, main PVT, autoimmune disease
RATIONALE-301 (3), tislelizumab	14.3 (10.8–18.5)	5.4 (3.2–8.4)	15.9 (13.2–19.7)	14.1 (12.6–17.4)	2.1 (2.1–3.5)	3.4 (2.2–4.1)	Inclusion: histologically confirmed HCC, unresectable HCC, BCLC B or C, Child Pugh A, no previous sistemic therapy Exclusion: main PVT

CI, confidence interval; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; PVT, portal vein thrombosis.

Tislelizumab stands out from sorafenib for its safety profile, with fewer grade 3 or higher adverse events. Its profile appears favorable and shows manageable adverse events consistent with previous studies of PD-1 inhibitors across different malignancies (7). Toxicity was manageable, with grade 3/4 adverse events reported in 48.2% of tislelizumab arm and 65.4% of sorafenib once. The most common immune-related adverse events registered in the tislelizumab arm were hypertransaminasemia (5.3%) and hypothyroidism (5.3%). This is a crucial aspect for maintaining patient quality of life during treatment.

A cost-effectiveness analysis is not included in the study; however, a recent evaluation has demonstrated that tislelizumab-based treatment should be the preferred choice over other first-line therapeutic alternatives for unresectable HCC (8). In China (9), tislelizumab therapeutic regimen had an incremental cost-effectiveness ratio of $22,869.64 per quality-adjusted life year (QALY), due to an increased QALYs by 0.568, representing a cost-effectiveness advantage compared to sorafenib.

Recently, in at health-related quality of life (HRQoL) analysis in the RATIONLE-301 population (10), tislelizumab demonstrated a superior profile in terms of HRQoL compared to sorafenib as first-line therapy, particularly in physical functioning and fatigue. Patients treated with tislelizumab maintained overall HCC symptom control, whereas symptoms worsened for those receiving sorafenib.

In summary, the RATIONALE-301 study highlights the evolving landscape of HCC treatment, with immune checkpoint inhibitors (ICIs) emerging as a promising therapeutic approach alongside existent systemic or locoregional treatments.

Nevertheless, it is essential to interpret the findings from RATIONALE-301 within the broader context of HCC management: despite the encouraging results, a large portion of patients does not benefit from tislelizumab and the gap between responder and non-responder patients seems to be higher than in other ICIs-based regimens. In *Table 1*, differences between tislelizumab and the immunotherapy regimens currently available and approved

by the EMA or FDA are shown.

Although there are no head-to-head studies of the existing immunotherapy, a comparison of the registration studies reveals that tislelizumab appears to be a step behind the alternatives, particularly atezolizumab-bevacizumab. ORR evaluation offers the most significant difference: 14.3% (95% CI: 10.8–18.5%) for tislelizumab versus 27.3% (95% CI: 22.5–32.5%) for atezolizumab-bevacizumab. The difference is also evident in terms of OS: 15.9 months (95% CI: 13.2–19.7) versus 19.2 months (95% CI: 17.0–23.7) and PFS: 2.1 months (95% CI: 2.1–3.5) versus 6.9 months (95% CI: 5.7–8.6) in favor to atezolizumab-bevacizumab.

Some of the differences showed in *Table 1*. can also be attributed to distinct characteristics of the studied population. The exclusion criteria of the CARES-310 study are notably more stringent compared to others and this choice, influenced also by the pharmacological characteristics of the drugs under study, results in a selected population with a better baseline prognosis. Furthermore, the atezolizumab-bevacizumab-based treatment and tremelimumab-durvalumab-based treatment are reserved for patients without complications due to portal hypertension, such as patients with a high risk of variceal bleeding or patients with meaningful ascites or with main PVT. The RATIONALE-301 study features significantly wider inclusion criteria. has much broader inclusion criteria. The lower ORR, OS, and PFS observed with tislelizumab must be interpreted considering that the study doesn't have the limitations of a strictly selected study population.

However, drawing conclusions based on a comparison of the published studies could be speculative, even if the inclusion criteria of the study population are quite similar. Given the current circumstances merely comparing trial results cannot be considered a key factor in the decision-making process for the "best therapy"; at most, it can provide insight to encourage more head-to-head studies.

The landscape of new agents and combinations continues to expand. Indeed, combination therapy seems to offer added value to therapeutic success rather than single-drug-based treatment. Multi-arm studies will be needed to directly compare therapeutic regimens and future investigations should aim to explore the potential benefits of combining tislelizumab with other ICIs or other systemic therapies to further enhance treatment outcomes. Since their introduction into the therapeutic armamentarium for HCC, monotherapy with PD-1 inhibitors has not achieved significant success. Initially, nivolumab in the phase 3 trial CHECKMATE 459 (12) and subsequently pembrolizumab in the phase 3 trial KEYNOTE 240 (13) did not meet their primary endpoint of improving OS. Regarding RATIONALE-301, while the efficacy and safety profile of Tislelizumab offers promise for improving patient outcomes, many existing limitations could be addressed by further research, capitalizing on its full therapeutic potential, which should be improved by a drug-combining regimen. Some clinical trials, aimed at providing further results from combination treatment, have shown encouraging results. For instance, the tislelizumab plus lenvatinib regimen (14) reported an ORR of 28.4%, a median OS of 18.2 months, and a PFS of 7.4 months. These results indicate that the combination of tislelizumab with lenvatinib may offer superior clinical benefits compared to tislelizumab monotherapy.

Other trials are currently ongoing, e.g., tislelizumab plus regorafenib (15) that is providing promising insights for potential future applications in clinical practice.

Lastly, there is an urgent need to identify predictive biomarkers for treatment response and outcome assessment. Predictive biomarkers for HCC include PD-L1 expression, tumor-infiltrating lymphocytes (TILs), serum soluble PD-L1 (sPD-L1), AFP levels, neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, and cell-free tumor DNA (cfDNA). Although, results from the study of these biomarkers have been inconsistent (16). Further research into predictive biomarkers is essential for optimizing immunotherapy in HCC. Although efforts have been made to explore the predictive biomarkers for these therapies, satisfactory markers have not yet been identified.

In conclusion, since the pronounced superiority of the therapeutic combination proposed by IMBRAVE-150, a new paradigm has been established in the treatment of advanced HCC: a combination of PD-1/PD-L1 inhibitors with an antiangiogenic agent. This combination has revolutionized first-line treatment for advanced HCC. As discussed above, tislelizumab-based monotherapy could potentially address, with favorable outcomes, the limitations associated with treating patients with complications of portal hypertension. The RATIONALE-301 study, comparing tislelizumab with sorafenib, represents a further advancement in the field of HCC therapeutics and positions tislelizumab as a promising and alternative first-line systemic treatment of unresectable HCC and underscores the importance of continued innovation and collaboration in this field, but real-world studies are warranted to validate the findings of this trial in broader patient populations and clinical settings, ensuring the generalizability of results.

Immunotherapy is poised to revolutionize the management of HCC, offering renewed hope for patients battling this aggressive malignancy. Moving forward, real-world studies and further research into combination regimens and predictive biomarkers will be essential to fully capitalize on ICIs' therapeutic potential and to refine patient selection criteria. Immunotherapy continues to revolutionize HCC management, but ongoing investigation is crucial to address challenges and optimize its application in clinical practice. Patient selection, biomarker identification, and resistance mechanisms warrant further investigation to optimize its use.

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