COSMIC-312, a disappointing result—is that so surprising?

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The therapeutic management of advanced hepatocellular carcinoma (HCC) has radically changed in recent years with the advent of immune checkpoint inhibitors (ICIs), similar to other tumor pathologies (1). Robust clinical responses have been observed, and there is a strong rationale for the use of these agents for HCC. Chronic inflammation of the liver is related to viral infection, fat overload, iron overload, or the production of damage-associated molecular patterns (DAMPs) in alcoholic liver disease, and the proinflammatory cytokines that it generates [interleukin (IL)-2, IL-7, IL-12, IL-15 and interferon-gamma (IFN-γ)] impair the immunotolerance of the liver and promote carcinogenesis (2). In cancer, tumor cells use various mechanisms to disrupt an immune response, either by eluding recognition (insensitivity to IFN-γ and decreased expression of major histocompatibility complex class I molecules) or by making the tumor microenvironment highly immunosuppressive. This is achieved by the recruitment of immunosuppressive cell populations (myeloid-derived suppressor cells, regulatory T cells), the expression of programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitory immune checkpoint molecules on T cells, the secretion of soluble factors (IL-10, tumor growth factor β), a decrease in functional dendritic cells, and the promotion of pro-tumor inflammatory factors (3). However, single-agent ICI treatment provides benefits in less than 20% of patients (4). Tumor-infiltrating lymphocytes (TILs) play a key role in this antitumoral response, but there is variability among patients. A previous study identified a subgroup among 228 resected HCCs that corresponded to an "immune class"; this subgroup accounted for 25% of cases, and was characterized by the presence of tumor-infiltrating T cells, PD-1 signaling, and the expression of genes induced by the interferon signaling pathway (5). Logically, combination therapies have emerged as new therapeutic strategies, with response rates exceeding 30% in preliminary studies (6). Furthermore, the programmed-death ligand 1 (PD-L1) status does not appear to be a decisive factor in HCC.

Angiogenesis contributes to immunosuppression via endothelial cells in the tumor microenvironment by regulating tumor leukocyte infiltration and through PD-L1 coinhibitory molecule expression. Additionally, it contributes through a direct effect of proangiogenic factors, such as vascular endothelial growth factor A (VEGFA), by impairing dendritic cell maturation and $CD8^+$ T-cell tumor infiltration, and by increasing the number of regulatory T cells (7). First, the anti-PD-L1 antibody atezolizumab in combination with the anti-VEGFA antibody bevacizumab demonstrated its superiority to sorafenib in first-line systemic therapy. The IMbrave 150 trial demonstrated a statistically significant benefit in overall survival (OS) and progression-free survival (PFS) (8). More recently, results from the combination of durvalumab, another anti-PD-L1 antibody, and tremelimumab, an anti-CTLA-4 antibody, were also positive in patients with advanced HCC (9). Multikinase inhibitors (MKIs) inhibit VEGF and enhance the cytotoxic lymphocyte response. They also normalize

vascularization, thus increasing leukocyte infiltration (10) and supporting a synergistic antitumor effect. Therefore, trials testing ICI-MKI combinations are warranted. Moreover, MKI efficacy is time limited, as opposed to the durable control sometimes observed with ICIs. Thus, it seems relevant to combine these treatments. Preliminary studies using antiangiogenic MKIs in combination with ICIs have shown interesting results. For example, the phase Ib study of lenvatinib plus pembrolizumab, an anti-PD-1 antibody, showed a confirmed objective response rate of 36.0% [per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1] and a median PFS of 8.6 months in a population of one hundred Barcelona Clinic Liver Cancer (BCLC) B/C stage HCCs, with preserved liver function (11).

The COSMIC-312 study (12) is a phase III trial that started in 2018 and aimed to compare the standard of care at that time, which was the MKI sorafenib, to the combination of atezolizumab and cabozantinib. Cabozantinib specifically targets vascular endothelial growth factor receptor (VEGFR)-2, similar to other MKIs, but stands out by additionally targeting AXL and c-MET kinases involved in sorafenib resistance (13). The participants (similar to other phase III trials, *Table 1*) were randomized 2:1:1 to receive cabozantinib at 40 mg once daily plus atezolizumab at 1,200 mg every 3 weeks, single-agent sorafenib at 400 mg twice daily, or cabozantinib monotherapy at 60 mg once daily. In the planned primary analysis, there was a significant reduction of 37% in the risk of disease progression or death compared with sorafenib [hazard ratio (HR), 0.63; 95% confidence interval (CI): 0.44–0.91; P=0.0012]. However, there was no OS benefit with the combination. The radiological response rate was less than 20%, which is comparable to that of MKI (14) or ICI monotherapy (4) (*Table 1*). Conversely, the median OS with cabozantinib/atezolizumab and sorafenib in the subset of patients with hepatitis B virus (HBV) infection (n=191) within the intent-to-treat population was 18.2 and 14.9 months, respectively (HR, 0.53; 95% CI: 0.33–0.87) (12). Additionally, one recent randomized phase III trial assessing a new ICI-MKI combination in a population mainly composed of HBV-related HCC showed a survival benefit compared to sorafenib (HR, 0.62; 95% CI: 0.49–0.80) (15).

How can this result be explained? Certainly, there may be an impact of treatment post disease progression; 20% of patients in the combination arm and 37% in the sorafenib arm received a second line of systemic therapy. Based on the dose reduction of cabozantinib, the toxicity mainly related to the antiangiogenic agent probably contributed, as the average daily dose was 24.2 mg (12). However, MKI-related toxicities have been recognized for more than 10 years and are now better managed by clinicians (16). In metastatic renal cell carcinoma, several ICI-MKI combinations have shown a benefit in OS and PFS (17-19), as opposed to the atezolizumab/bevacizumab combination (20). This is despite the occurrence of adverse events > grade 3 in more than 50% of cases. Moreover, failure does not only concern the cabozantinib/atezolizumab combination. Indeed, despite some improvements in OS and PFS, pembrolizumab and lenvatinib compared with lenvatinib monotherapy in patients with unresectable HCC in the phase 3 LEAP-002 trial missed the threshold for significance (21).

These results are not unexpected since no predictive biomarkers of response to immunotherapy are available. Immunohistochemical expression of PD-L1 in tumor and immune cells has shown limits in HCC, with no correlation between PD-L1 expression and increased survival (4,6,21). The various positivity thresholds (number of marked cells/number of total cells) used may have contribute to these results. Molecular biomarkers of immunotherapy response are emerging. Tumor gene expression profiling is one example of this, as it measures the expression of several hundred genes involved in the immune response simultaneously. The tumor inflammation signature (TIS), which includes markers related to interferon production, tumor antigen presentation, chemokine secretion for recruitment, cytotoxic activity mediated by lymphocytes and natural killer cells, is associated with prolonged PFS in patients treated with anti-PD-1 antibody (22).

Do we need to consider the underlying liver disease? This question deserves careful attention. A recent large real-life study comparing atezolizumab/bevacizumab with lenvatinib as first-line systemic therapy for unresectable HCC emphasized the impact of underlying liver disease, with a probable advantage of lenvatinib in the population with nonalcoholic steatohepatitis (NASH) (23). A subgroup analysis of the IMbrave150 trial suggested a lower efficacy of atezolizumab/bevacizumab than sorafenib in the virus-free population (30% of enrollment) (HR, 0.91; 95% CI: 0.51–1.60) compared with the population with viral disease [HBV: HR, 0.51; 95% CI: 0.32–0.81; hepatitis C virus (HCV): HR, 0.43; 95% CI: 0.22–0.87]. A meta-analysis of the three controlled trials, IMbrave150, Checkmate-459, and KEYNOTE-240, found comparable results (24). In this article, preclinical studies showed that in NASH-affected livers, $CD8^+$ T cells are increased, have a distinct phenotype, impair immune surveillance and show a protumoral and

Table 1 Randomized phase 3 trials of first-line treatment in patients with unresectable hepatocellular carcinoma

Variables	Positive trials		Negative trials			Noninferiority
	IMbrave 150 (NCT03434379)	HIMALAYA (NCT03298451)	COSMIC-312 (NCT03755791)	LEAP-002 (NCT03713593)	CheckMate 459 (NCT02576509)	REFLECT (NCT01761266)
Agents	Atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGFA) *vs.* sorafenib (MKI)	Tremelimumab (anti-CTLA-4) plus durvalumab (anti-PD-L1) (STRIDE regimen) *vs.* sorafenib (MKI) *vs.* durvalumab (anti-PD-L1)	Cabozantinib (MKI) plus atezolizumab (anti-PD-L1) *vs.* sorafenib (MKI) *vs.* cabozantinib (MKI)	Lenvatinib (MKI) plus pembrolizumab (anti-PD-1) *vs.* lenvatinib (MKI)	Nivolumab (anti-PD-1) *vs.* sorafenib (MKI)	Lenvatinib (MKI) *vs.* sorafenib (MKI)
Population	HBV: 49%; HCV: 21%; nonviral: 30% (CP-A 100%; PS 0/1 100%)	HBV: 31%; HCV: 28%; nonviral: 41% (CP-A 100%; PS 0/1 100%)	HBV: 30%; HCV: 28%; nonviral: 42% (CP-A 100%; PS 0/1 100%)	HBV: 48.6%; HCV: 23.8%; nonviral: 30% (CP-A 100%; PS 0/1 100%)	HBV: 31%; HCV: 23%; nonviral: 45% (CP-A 98%; PS 0/1 100%)	HBV: 50%; HCV: 23%; nonviral: 27% (CP-A 99%; PS 0/1 100%)
	BCLC B/C: 15%/82% (MVI 38%; ES 63%)	BCLC B/C: 19.6%/80.4% (MVI 26%; ES 53%)	BCLC B/C 33%/67% (MVI 34%; ES 54%)	BCLC B/C 21.5%/78.5% (MVI 18%; ES 63%)	BCLC B/C 14%/82% (MVI 33%; ES 60%)	BCLC B/C 21%/79% (MVI 21%; ES 61%)
	AFP >400 ng/mL 38%	AFP >400 ng/mL 37%	AFP >400 ng/mL 34%	AFP >400 ng/mL 30%	AFP >400 ng/mL 33%	AFP >200 ng/mL 43%
Overall survival	[ATZ + BVZ] 19.2 mo *vs.* [Sor] 13.4 mo; HR 0.66 (0.52–0.85)	[T300 + D] 16.4 (14.2–19.6) mo *vs.* [Sor] 13.8 (12.3–16.1) mo; HR 0.78 (0.65–0.92) [D] 16.6 (14.1–19.1) mo *vs.* [Sor]; HR 0.86 (0.73–1.03)	[CBZ + ATZ] 15.4 (13.7–17.7) mo *vs.* [Sor] 15.5 (12.1–NE) mo; HR 0.90 (0.69–1.18)	[Len + Pem] 21.2 (19.0–23.6) mo *vs.* [Len] 19.0 (17.2–21.7) mo; HR 0.840 (0.708–0.997)	[Nv] 16.4 (13.9–18.4) mo *vs.* [Sor] 14.7 (11.9–17.2) mo; HR 0.85 (0.72–1.02)	[Len] 13.6 (12.1–14.9) mo *vs.* [Sor] 12.3 (10.4–13.9) mo; HR 0.92 (0.79–1·06)
Progression-free survival	[ATZ + BVZ] 6.8 (5.7–8.3) mo *vs.* [Sor] 4.3 (4.0–5.6) mo; HR 0.59 (0.47–0.76)	[T300 + D] 3.78 (3.68–5.32) mo *vs.* [Sor] 4.07 (3.75–5.49) mo; HR 0.90 (0.77–1.05) [D] 3.65 (3.19–3.75) mo *vs.* [Sor]; HR 1.02 (0.88–1.19)	[CBZ + ATZ] 6.8 (5.6–8.3) mo *vs.* [Sor] 4.2 (2.8–7.0) mo; HR 0.63 (0.44–0.91) [CBZ] 5.8 (5.4–8.2) mo *vs.* [Sor]; HR 0.71 (0.51–1.01)	[Len + Pem] 8.2 (6.3–8.3) mo *vs.* [Len] 8.1 (6.3–8.3) mo; HR 0.834 (0.712–0.978)	[Nv] 6.8 (5.6–8.3) mo *vs.* [Sor] 4.2 (2.8–7.0) mo; HR 0.63 (0.44–0.91)	[Len] 7.4 (6.9–8.8) mo *vs.* [Sor] 3.7 (3.6–4.6) mo; HR 0.65 (0.56–0.77)
Objective response (RECIST 1.1)	[ATZ + BVZ] 29.8%; [Sor] 11.3%	[T300 + D] 20%; [Sor] 5%; [D] 17%	[CBZ + ATZ] 11%; [Sor] 4%; [CBZ] 6%	[Len + Pem] 26.1%; [Len] 17.5%	[Nv]15%; [Sor] 7%	[Len] 18.8%; [Sor] 6.5%
Disease control rate	[ATZ + BVZ] 73.6%; [Sor] 55.3%	[T300 + D] 60%; [Sor] 60.7%; [D] 54.8%	[CBZ + ATZ] 78%; [Sor] 65%; [CBZ] 84%	[Len + Pem] 81.3%; [Len] 78.4%	[Nv] 55%; [Sor] 58%	[Len] 72.8%; [Sor] 59.0%
Grade 3 or 4 adverse events	[ATZ + BVZ] 56.5%; [Sor] 55.1%	[T300 + D] 50.5%; [Sor] 52.4%; [D] 37%	[CBZ + ATZ] 64%; [Sor] 46%; [CBZ] 60%	[Len + Pem] 61.5%; [Len] 56.7%	[Nv] 22%; [Sor] 49%	[Len] 75%; [Sor] 67%

AFP, alpha-fetoprotein; ATZ, atezolizumab; BCLC, Barcelona Clinic Liver Criteria; BVZ, bevacizumab; CBZ, cabozantinib; CP, Child-Pugh; CTLA-4, cytotoxic T-lymphocyte antigen-4; D, durvalumab; ES, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; Len, lenvatinib; MKI, multikinase inhibitor; mo, months; MVI, macrovascular invasion; Nv, nivolumab; PD-1, programmed death receptor-1; PD-L1, programmed-death ligand 1; PS, performance status; Pem, pembrolizumab; RECIST, Response Evaluation Criteria in Solid Tumors; Sor, sorafenib; T, tremelimumab; VEGF, vascular endothelial growth factor..

immunosuppressive transcriptional signature upon anti-PD-1 treatment.

In summary, ICIs and combination therapies have sustainably changed the therapeutic strategy for HCC; a major first step has been reached. Therapeutic advances will come from the systematic analysis of tumor tissue to capture the heterogeneity of HCC, as reflected in molecular classifications (25) that define subgroups based on oncogenic alterations, deregulated signaling pathways, epigenetic modifications and immune response. Additionally, advances will stem from the use of relevant biomarkers correlated with response to ICIs.

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