Editorial Commentary

Simultaneous blockage of the PD-1/PD-L1 axis and VEGF pathway are clinically relevant in hepatocellular carcinoma therapy

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Hepatocellular carcinoma (HCC) is a frequent cancer, fourth cause of death by cancer worldwide (1). A wide proportion of HCC patients becomes eligible to systemic therapies during the history of their disease. Before the emergence of immune-checkpoint inhibitors (ICI)-based regimens, two tyrosine kinase inhibitors (TKI), sorafenib and lenvatinib, had been approved for first line systemic therapy (1L) (2). Two other TKIs (regorafenib and cabozantinib) and a monoclonal antibody (ramucirumab) targeting the vascular endothelial growth factor receptor 2 (VEGFR-2) receptor, have shown positivity in pivotal phase-3 trials after 1L sorafenib failure (3-5). All these drugs significantly improved the outcome of patients as assessed by increase of median overall survival (OS), although with rare long-term survivors and exceptional prolonged complete responses with subsequent recoveries. ICI strategies have changed the paradigm of HCC systemic treatments with improvement of OS, and allowing a proportion of patients being long-term survivors, with a possibility of recovery.

Monotherapies of ICI failed the primary endpoints in phase-3

CheckMate-459 randomized in 1L nivolumab (PD-1 inhibitor) to sorafenib (6). Nivolumab showed 15% objective response rate (ORR) per RECIST v1.1, 23.3 months median duration of response (DOR) [95%confidence interval (CI) 3.1–34.5+] months, and 55% disease control rate (DCR) (*Table 1*). However, OS or progression-free survival (PFS) were disappointing *vs.* sorafenib: (I) 16.4 median OS (95% CI: 13.9–18.4) *vs.* 14.7 (95% CI: 11.9–17.2) months, HR 0.85 (95% CI: 0.72–1.02), P=0.0752; (II) 3.7 median PFS (95% CI: 3.1–3.9) *vs.* 3.8 (95% CI: 3.7–4.5) months, HR 0.93 (95% CI: 0.79–1.10) (*Table 1*). Safety of nivolumab was remarkable *vs.* sorafenib: less grade-3/4 treatment-related adverse events (TRAE) (22% *vs.* 49%), rate of withdrawal due to adverse event (AE) of 9% *vs.* 11%, and better quality of life with nivolumab per FACT Hep total.

Keynote-240 randomized in 2L after failure of sorafenib, pembrolizumab (PD-1 inhibitor) to placebo (8). Pembrolizumab showed 18.3% ORR per RECIST v1.1, 13.8 DOR (95% CI: 1.5+–23.6+) months, and 62% DCR (*Table 1*). Outcomes were also disappointing since the OS and PFS co-primary end-points did not met statistical significance: (I) OS 13.9 (95% CI: 11.6–16.0) *vs.* 10.6 (95% CI: 8.3–13.5) months, HR 0.78 (95% CI: 0.61–0.99), P=0.0238; (II) PFS 3.0 (95% CI: 2.8–4.1) *vs.* 2.8 (95% CI: 1.6–3.0) months, HR 0.72 (95% CI: 0.57–0.90), P=0.0022 (*Table 1*). Like nivolumab, pembrolizumab showed rather good tolerance with 18.3% grade-3/4 TRAE, and 6.5% of treatment withdrawal due to AE, and preserved quality of life (14).

ICI-based combination therapies have brought exciting data in the treatment of HCC

It has been demonstrated a synergy between PD-1 or PD-

Table 1 Summary of efficacy parameters in the ICI-based therapies

Therapy	ORR RECIST 1.1	DCR RECIST 1.1	Median PFS RECIST 1.1, months (95% CI)	Median OS, months (95% CI)	Trial (phase) (Ref)
Nivolumab	15%	55%	3.7 (3.1–3.9)	16.4 (13.9–18.4)	CheckMate-459 (phase-3) (6)
Nivolumab + ipilimumab	32%	54%	Not available	22.8 (9.4–NE)	CheckMate-040 (phase-1/2) (7)
Pembrolizumab	18.3%	62.2%	3.0 (2.8–4.1)	13.9 (11.6–16.0)	Keynote-240 (phase-3) (8)
Pembrolizumab + lenvatinib	36%	88%	8.6 (7.1–9.7)	22 (20.4–NE)	STUDY-116 (phase-1b) (9)
Atezolizumab + bevacizumab	30%	74%	6.9 (5.7–8.6)	19.2 (17.0–23.7)	IMbrave-150 (phase-3) (10,11)
Durvalumab + tremelimumab	24%	45.3%	2.2 (1.9–5.4)	18.7 (10.8–27.3)	STUDY-22 (phase-1/2) (12)
Sintilimab + IBI305	21%	73%	4.6 (4.1–5.7)	NE (NE–NE)	ORIENT-32 (phase-2/3) (13)

ICI, immune-checkpoint inhibitors; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; NE, not estimable.

L1 inhibitors and anti-angiogenic agents (AAA) that can silence the immunosuppressive properties of the tumor microenvironment, for instance by inhibition of Treg and MDSC immunosuppressive cells (15,16). IMbrave-150 is the first pivotal phase-3 trial to have demonstrated clinical relevance of ICI-based therapy on the outcome of HCC patients (10,11). The combination of atezolizumab (PD-L1 inhibitor) plus bevacizumab (AAA) was randomized *vs.* sorafenib in 1L. ORIENT-32, assessing the combination of sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib, is the second phase-3 of ICI-based combination showing a significant improvement of the outcome of HCC patients in 1L (13). IMbrave-150 and ORIENT-32 both associate a monoclonal antibody targeting VEGF (bevacizumab, and IBI305, a bevacizumab biosimilar) and an ICI targeting the PD-1/PD-L1 pathway: atezolizumab (PD-L1 inhibitor) and sintilimab (PD-1 inhibitor), respectively). This is a first potential advantage for ORIENT-32 since PD-1 inhibitors might be more efficient than PD-L1 inhibitors in a variety of tumors as reported in the meta-analysis of Duan *et al.* (the primary endpoint of the analysis being the difference in OS), although it remains to be demonstrated in phase-3 setting, especially in HCC (17).

Although it remains unreliable to compare two median OS from two different trials, we can argue that OS seems to be likely quite similar, but longer follow-up is needed in ORIENT-32 to get the median value of OS. In IMbrave-150, median OS was: (I) at the first intermediate analysis (10) (median follow-up, 8.6 months), not estimable (NE) in the ATEZO/BEV arm *vs.* 13.2 (95% CI: 10.4–NE) months in the SORAF arm, stratified HR 0.58 (0.42–0.79), P=0.0006; and (II) in updated data (11) (median follow-up 15.6 months), 19.2 (95% CI: 17.0–23.7) *vs.* 13.4 (95% CI: 11.4–16.9) months, stratified HR 0.66 (0.52–0.85), P=0.0009. By comparison in ORIENT-32, only data from the first intermediate analysis are available (median follow-up, 10 months), showing OS NE in the SINTI/IBI305 arm *vs.* 10.4 (95% CI: 8.5–NE) months in the SORAF arm, stratified HR 0.57 (95% CI: 0.43–0.75), P<0·0001.

ORIENT-32 was performed in 50 clinical sites in China, this geographical status giving 94% HBV-related HCC *vs.* 49% in the global IMbrave-150 trial, and 88% in the China cohort of IMbrave-150 (11). Stratification factors included in the Cox model were presence of macrovascular invasion or extrahepatic metastasis, baseline α-fetoprotein level (<400 *vs.* ≥400 ng/mL), and ECOG performance status (0 *vs.* 1) in ORIENT-32, and the same in addition to geographic area (Asia excluding Japan *vs.* Rest of the World) in IMbrave-150. Taking account only of the China cohort of IMbrave-150, likely closer to the population of ORIENT-32, the outcome of patients seems to be better than in the global population, with 24 OS (95% CI: 17.1–NE) months in the ATEZO/BEV arm *vs.* 11.4 (95% CI: 6.7–16.1) in the SORAF arm, stratified HR 0.53 (95% CI: 0.35–0.80). This discrepancy in geographic area and etiologic factors might also explain, at least in part, the better outcome of patient in the SORAF arm in the global population of IMbrave-150 (OS 13.4 months) *vs.* the China cohort of IMbrave-150 (OS

11.4 months) or of ORIENT-32 (OS 10.4 months). Comparing the global SHARP (18) and the specific Asian-Pacific (19) trials, it was clearly suggested that HCC patients under sorafenib have a worse outcome in the Asian population (OS in the SORAF arm, 10.7 months in SHARP *vs.* 6.5 months in Asian-Pacific trial).

Another surrogate marker of therapy efficacy could be PFS. This latter was improved both in ORIENT-32 and IMbrave-150 in the SINTI/IBI305 and ATEZO/BEV arms over sorafenib: 4.6 (95% CI: 4.1–5.7) *vs.* 2.8 (95% CI: 2.7–3.2) months, HR 0.56 (95% CI: 0.46–0.70), P<0.0001 in ORIENT-32; and 6.9 (95% CI: 5.7–8.6) *vs.* 4.3 (95% CI: 4.0–5.6) months, stratified HR 0.65 (95% CI: 0.53–0.81), P=0.0001 in IMbrave-150. In sub-group analysis, AFP <400 ng/mL seemed to be associated with a better outcome on both PFS and OS in the ATEZO/BEV arm. In ORIENT-32, AFP <400 ng/mL is rather associated with better outcome on PFS only but does not impact on OS. These data are in contrast with nivolumab monotherapy in CheckMate-459 where patients with AFP ≥400 ng/mL showed improved OS on the contrary of patients with AFP <400 ng/mL (6). These data illustrate the poor reliability of sub-group analysis in clinical trials due to the lack of statistic power and absence of specific design of the trial for each subgroup.

In ICI-based therapies for HCC, ORR seems to be a good surrogate marker of patient outcome. In IMbrave-150, ORR per RECIST v1.1 and mRECIST were 30% and 35%, respectively. In ORIENT-32, ORR tend to be lower at 21% and 24%, respectively by independent radiological review committee. DCR that takes account of both tumor responses and stabilizations, are quite the same per RECIST v1.1 and mRECIST, in IMbrave-150 (74% and 72%) and ORIENT-32 (72% and 73%). DOR was 18.1 (95% CI: 14.6–NE) months in the ATEZO/BEV arm of IMbrave-150 but hardly evaluable in the SINTI/IBI305 arm of ORIENT-32 [NE (95% CI: NE–NE)] due to the rather short follow-up.

An important point for systemic therapies in HCC is the safety and quality of life. Comparing ORIENT-32 to IMbrave-150, tolerance was quite similar with 43% *vs.* 33% of grade-3/4 TRAE, the treatment being interrupted due to AE in 49% of patients in the SINTI/IBI350 group *vs.* 49.5% of the ATEZO/BEV arm of IMbrave150, leading to trial withdrawal in 14% and 15.5% respectively. The median duration of treatment was of 7.0 (range, 0.7–15.2) months for sintilimab and 6.6 (range, 0.7–15.2) months for IBI305 whereas the median duration of treatment was 7.4 months with atezolizumab and 6.9 months with bevacizumab in IMbrave-150. Further, the median relative dose intensities of sintilimab and IBI305 were 93% (range, 33–108%), and 94% (range, 32–108%), respectively in ORIENT-32, and atezolizumab 98% (range, 54–104%) and bevacizumab 97% (range, 44–104%), for atezolizumab and bevacizumab respectively in IMbrave-150. ATEZO/BEV or SINTI/IBI305 giving rise to the same type of AE, it seems logical to observe that both ICI-based therapies allowed to have a significantly longer time to deterioration of quality of life over sorafenib.

Future ICI-based combinations

Results of other phase-3 trials assessing ICI-based combinations are pending with either PD-1/PD-L1 plus CTLA-4 inhibitors [nivolumab + ipilimumab in the CheckMate-9DW (NCT04039607), and durvalumab + tremelimumab in the HIMALAYA (NCT03298451)] or PD-1/PD-L1 inhibitors plus TKI (pembrolizumab + lenvatinib in the LEAP-002 (NCT03713593), and atezolizumab + cabozantinib in the COSMIC-312 (NCT03755791). If positive, these trials could completely change the paradigm of HCC therapy in a near future, and at the moment only data from phase-1/2 trials are available.

The phase-1b STUDY-116 (9) assessed the combination of pembrolizumab with lenvatinib, highlighting striking results in terms of tumor response parameters: 36% ORR per RECIST v1.1, and 88% DCR, which seems to be higher than with anti-PD-1/PD-L1 + anti-CTLA-4 or bevacizumab combinations (*Table 1*). The outcome of patients is very satisfactory with one of the best median OS at 22 (95% CI: 20.4–NE) months such as in nivolumab + ipilimumab combination (7), and a prolonged median PFS at 8.6 (95% CI: 7.1–9.7) months (*Table 1*). Safety seemed to be worse by comparison to nivolumab/ipilimumab combination since the rate of grade-3/4 TRAE was higher at 67% *vs.* 53%, but the incidence of AE leading to treatment withdrawal was lower 14% *vs.* 22%.

The phase-1/2 STUDY-22 trial (12) compared durvalumab + tremelimumab (one single high dose of 300 mg) *vs.* durvalumab *vs.* tremelimumab (750 mg Q4W for 7 courses, and thereafter Q12W) *vs.* durvalumab + tremelimumab (75 mg Q4W for 4 courses). The first arm showed the most interesting data with 24% ORR per RECIST v1.1, but low DCR at 45.3% (*Table 1*) such as ICI-based monotherapies (6,8), or nivolumab/ipilimumab combination (7). The outcome parameters are inferior to

those shown by ipilimumab/nivolumab or pembrolizumab/lenvatinib combinations: 18.7 median OS (95% CI: 10.8–27.3) months, and 2.2 median PFS (95% CI: 1.9–5.4) months (*Table 1*). Safety seemed to be better than with nivolumab/ipilimumab combination: 35.1% *vs.* 53% grade-3/4 TRAE, and 10.8% *vs.* 22% AE leading to trial withdrawal.

In the phase-1/2 Checkmate-040 (7), three schedules of nivolumab/ipilimumab combination were tested and the most promising, in terms of ORR and OS, was NIVO-1/IPI-3: induction with nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) Q3W for 4 cycles, and subsequent consolidation with nivolumab (240 mg) Q2W. Efficacy data were exciting with 32% ORR per RECIST v1.1, but still low DCR of 54% such as in monotherapies of ICI (*Table 1*). OS was as high as pembrolizumab + lenvatinib at 22.8 (95% CI: 9.4–NE) months (*Table 1*). However, safety seems debatable due to the high rate of grade-3/4 TRAE at 53%, and the high percentage (22%) of patients withdrawing the treatment because of AE.

Conclusions

The systemic treatment of HCC has been revolutionized by the development of ICI-based combination strategies. Data from several phase-3 trials with different types of combinations are pending, but so far, IMbrave-150 has been the first phase-3 trial proving the substantial benefit of combining a PD-L1 inhibitor plus bevacizumab, an AAA. The presently discussed study ORIENT-32 published this year, has brought another phase-3 trial demonstrating very likely the same efficacy and safety of a combination with a PD-1 inhibitor (sintilimab) plus a bevacizumab biosimilar (IBI305). Thus, this represents a new tool for HCC therapy, keeping in mind that data of the new types of ICI-based combinations in phase-3 are urgently expected to build the new paradigms of HCC therapy in a near future.

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