Editorial Commentary

Anti-PD1 monotherapy in hepatocellular carcinoma: a step forward or already behind?

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In *The Lancet Oncology*, Qin *et al*., presented the promising results of a multicentre, open-label, parallel-group, randomised, phase 2 trial in a Chinese population, exploring the efficacy and safety of two different application schedules of the anti-PD-1 monoclonal antibody Camrelizumab as post-progression treatment of advanced hepatocellular carcinoma (1). Eligible patients were either refractory or intolerant to first line systemic therapy. Different from other studies on PD-1 inhibitors in HCC, HBV infection was identified in more than 80% of cases, which reflects the typical HCC epidemiology in China. Noteworthy is the high prevalence of other baseline characteristics which usually indicate a poor prognosis: 95% of patients had Barcelona Clinic Liver Cancer (BCLC) stage C HCC, 12% had macrovascular invasion, 82% showed extrahepatic spread and >50% an alpha-fetoprotein (AFP) blood level of ≥400 ng/mL. After a median follow-up of 12.5 months [inter-quartile range (IQR) 5.7–15.5], the objective response rate (ORR; primary endpoint) and the 6-month overall survival were 14.7% (95% CI: 10.3–20.2%) and 74.4% (95% CI: 68.0–79.7%), respectively. Median overall survival (OS) and progression free survival (PFS) were 13.8 months (95% CI: 11.5–16.6) and 2.1 months (95% CI: 2.0–3.2), respectively. However, OS analysis is still immature with only 53% of patients who had died at cut-off date. Interestingly, of the 161 patients who had initial radiological disease progression per investigator, 95 (59%) continued camrelizumab treatment (monotherapy or in combination with, or followed by, other therapy). Subsequent treatments received by the 66 patients who discontinued treatment with the immune checkpoint inhibitor included any kind of molecularly targeted therapy in 41%. Patients who continued camrelizumab had an overall survival probability at 6 months of 74% compared to only 54.4% in those patients who discontinued camrelizumab. The most common treatment-emergent immune-related adverse event was reactive cutaneous capillary endothelial proliferation (RCCEP) (67% of grade 1–2, none of grade 3) which represents a drug-specific, early onset cutaneous side-effect, apparently associated with treatment response on post-hoc analyses (1). Although further investigations are needed, the same association with response was recently observed in a phase I study with camrelizumab (2) in a variety of solid tumours and in a post-hoc exploratory analysis from the phase III ESCORT trial investigating camrelizumab *vs.* investigator´s choice as second line treatment in squamous cell esophageal carcinoma (3). Other toxicities were as expected from this class of drugs. Since the primary endpoint analysis of ORR is promising and the safety profile is manageable, camrelizumab might be considered as a potential post-progression treatment option for advanced HCC, especially

in a population with poor prognostic characteristics, according to authors' opinion (1). In our opinion, this statement deserves some discussion in the rapidly advancing field of immune-therapy for HCC.

HCC is the most common type of primary liver cancer. The target organ of HCC is a central player of immunomodulation. It ensures protection of the organisms by removing continuously a large spectrum of pathogens, microbe-associated molecular patterns (MAMPs) and damage associated molecules (DAMPs) while maintaining immune-tolerance to non-pathological or constant inflammatory stimuli. Deregulation of this tightly controlled immunological network can lead to liver disease, including liver cirrhosis and liver cancer. The multitude of the hepatic resident innate and adaptive immune cells (Kupffer cells, dendritic cells, liver sinusoidal endothelial cells, NK T cells, γδ T cells, Ito cells, CD8+ and Cd4+ T cells) and their swinging phenotype between immune-activation and immune-tolerance constitute the background for the ongoing paradigm shift towards immunotherapy in HCC (4). Camrelizumab is a high affinity monoclonal antibody directed against the negative immune-regulatory human cell surface receptor programmed death-1 (PD-1). By blocking the binding of PD-1 on activated T lymphocytes, B and natural killer (NK) cells to its ligands programmed cell death ligand 1 (PD-L1), which can be found to be overexpressed on cancer cells, and programmed cell death ligand 2 (PD-L2), primarily expressed on antigen presenting cells (APCs), it restores immune function against tumor cells or pathogens. Compared to the PD-1 inhibitors, nivolumab and pembrolizumab, camrelizumab shows persistent receptor occupancy and binds to a different epitope leading to subtle differences in signaling regulation. Of note, it also shows a potent agonism on vascular endothelial growth factor receptor 2 (VEGFR2) being most probably responsible for its highly specific vascular neo-genesis side effect (hemangioma proliferation). However, the fact that it affects preferably the skin and not mucosal tissues, downsizes the risk for bleeding and for critical drug tolerability (5-7). The paramount question, nevertheless, is if we need another mono-immunotherapy agent as second line treatment: does camrelizumab represent a novel cutting-edge strategy?

Although formal comparisons among different studies should not be done, both pembrolizumab and nivolumab demonstrated interesting activity in second line treatment of advanced HCC (8-10). The ORR with pembrolizumab in the phase 2 Keynote-224 (17%, 95% CI: 11–26%) and in the corresponding phase 3 Keynote-240 (18.3%, 95% CI: 14–23.4%) tended to be higher than the ORR reported with camrelizumab. Of note, more favorable baseline characteristics of patients included in the Keynote studies may explain these differences.(8,9) With an ORR of 13% in the chronic hepatitis related advanced HCC subgroup of Keynote-224 (45% of the overall population) no difference in terms of anti-tumor activity seems to exist between pembrolizumab and camrelizumab for this subgroup of patients (8). In Keynote-240, pembrolizumab unfortunately did not reach its predetermined level of statistical significance for an improvement in survival, although at the two exploratory sensitivity analyses, which evaluated OS adjusting for the use of subsequent treatment, the HR for OS was 0.65. An explanation is that the control arm performed better than expected, probably due to the increasing use of effective post-progression therapies (9,11-13). In a phase 1/2 study, also nivolumab showed noteworthy and durable responses both in treatment-naïve patients and in patients progressing on sorafenib (ORR 21–23%; 9-month survival rate of 74%). Especially, the duration of response was impressive. Albeit the study was not powered for statistical comparison between patients with different HCC etiologies including viral hepatitis, responses seemed to be consistent among the different HCC groups. In the subgroup of 51 HBV positive patients presenting with extrahepatic spread, macrovascular invasion and high levels of α-fetoprotein, that were comparable with those of the Chinese population treated with camrelizumab, an ORR of 14% and a 6 months OS of 84% were observed, which are in line with the efficacy of all other anti-PD1 inhibitors (10). Nevertheless, the randomized controlled phase III Checkmate-459 study, comparing nivolumab with sorafenib in first-line advanced HCC, also did not reach the predefined threshold of statistical significance for better OS. A relevant difference in terms of higher response rates with nivolumab did not translate into better OS (median 16.4 *vs.* 14.7 months); nonetheless, like in the Keynote-240, the control arm performed better as expected, probably due to the subsequent use of systemic therapies, including immunotherapy (14). Therefore, we might conclude that the OS benefit achieved by immune-checkpoint monotherapy is meaningful, even more when considering the better quality of life reported by patients in the immunotherapy arms. It should be considered, though, that 30–40% of patients did not respond at all to immunotherapy, and disease progressed quickly in some cases. Therefore, the lack of good predictive markers is

one of the major limitations for the successful use of PD-1 inhibitors as monotherapy, but the fundamental one is the forthcoming amendment of our therapeutic strategy due to the results of the Imbrave-150 trial (15).

The Vascular endothelial growth factor-A (VEGF-A) is—for more than a decade—a major therapeutic target in HCC first line therapy (16-18). Moreover, it is well known that tumor angiogenesis and immunosuppression in cancer pathogenesis are connected: tumor dissemination requires neo-vasculature and suppression of excessive inflammation (19). Tumor cells and endothelial cells release abundant amounts of VEGF-A, which activates and recruits the immune-suppressive cell department including tumor-associated macrophages, regulatory T-cells (T-REGs) and myeloid-derived suppressor cells (MDSC). This contribute to the immune-escape mechanisms of HCC. Thus, the disruption of angiogenesis, which has become a cornerstone of HCC treatment, theoretically enhances the efficacy of immune–based cancer therapies, the new avant-garde of the HCC therapeutic scenario. Experimental evidence shows an improvement of antigen presentation by dendritic cells, an increase of T-cell priming and inhibition of T-REGs by reducing the release of inhibitor cytokines, like TGF-β and IL-10, and eventually a regulation of the T-lymphocyte traffic from lymph nodes to tumor site (20,21). Clinically, the combination of anti-angiogenics and immune-checkpoint inhibitors in HCC has revealed outstanding results (22-24). Recently, atezolizumab, a PD-L1 targeting monoclonal antibody, and bevacizumab, a VEGF-A directed agent, have demonstrated superiority in terms of ORR and OS in treatment-naïve advanced HCC patients compared with standard of care. A notable ORR of 27.3% *vs.* 11.9% translated into a better PFS (6.8 *vs.* 4.3), a considerable duration of response, which was longer than 6 months in 87.6%. The median OS was not reached in the experimental arm *vs.* 13.2 months in the control arm (HR 0.58, 95% CI: 0.42–0.79; p<0.001) with a rapid achievement of the plateau in the atezolizumab plus bevacizumab group; estimated rates of survival at 6 and 12 months were 84.8% and 67.2% *vs.* 72.2% and 54.6%. The safety of immune-checkpoint inhibition and anti-angiogenesis was adequate and in terms of number of reported events comparable with sorafenib. The trial is even more noteworthy as the study population shows high-risk features: 38% of macro-vascular invasion, including invasion of the major portal trunk, which is often an exclusion criterion in advanced HCC first line trials; 38% of patients showed alpha-fetoprotein higher than 400 ng/mL; 49% had an underlying chronic HBV infection, 63% showed extrahepatic spread of disease. The magnitude of the effect in co-primary endpoints in the Chinese population, characterized by higher proportion of the abovementioned risk factors (88% HBV positive and 86% in BCLC-C stage), was clinically meaningful and consistent with that of the global population (HR for OS: 0.44 *vs.* 0.58 and for PFS: 0.6 *vs.* 0.59) (15). The early separation of the OS curves, maintained over the time, has to be highlighted as well, despite a higher proportion of patients in the sorafenib group receiving subsequent treatment, including immunotherapy.

We might also speculate about the mechanism of action of camrelizumab: its agonism on VEGFR2 may contradict the strong rationale and the results derived from the combination of antiangiogenic therapies and immune-checkpoint inhibitors previously shown. In line with these considerations, the combination of camrelizumab with apatinib (anti-VEGFR2) in a phase 1b trial that included 43 patients affected by HCC and gastroesophageal cancers obtained an ORR of 30.8% (95% CI: 17.0–47.6%); moreover, in 50% of HCC patients a partial response was observed (24). A trial aiming to validate these results in the first line setting is ongoing (see *Table 1*).

In summary, the perspectives derived from Imbrave-150 in the first line setting and the awaited results from ongoing studies of combination therapies are expected to change the HCC therapeutic algorithms profoundly. The cruising speed of this motion is so high that goals like those achieved by anti-PD1 monotherapy with camrelizumab after progression to sorafenib, seem to be already out of date.

Table 1 Selected ongoing trials in HCC treatment

Clinical trial identifier	Setting	Phase	Treatment arm	Primary endpoint	Recruiting	Target accrual (pts)
NCT03755791 Cosmic-312	First line	III	Cabozantinib + Atezolizumab *vs*. Sorafenib	PFS, OS	Yes	740
NCT03298451 Himalaya	First line	III	Durvalumab + Tremelimumab *vs*. Sorafenib	OS	No	1,310
NCT03713593 LEAP-002	First line	III	Lenvatinib + Pembrolizumab *vs*. Lenvatinib	PFS, OS	No	750
NCT03764293	First line	III	Apatinib + Camrelizumab *vs*. Sorafenib	PFS, OS	Yes	510
NCT04039607 CheckMate 9DW	First line	III	Nivolumab + Ipilimumab *vs*. Sorafenib or Lenvatinib	OS	Yes	1,084
NCT03412773 Rationale-301	First line	III	Tislelizumab *vs*. Sorafenib	OS	No	674
NCT03778957 Emerald-1	First line in aLLD	III	TACE Durvalumab +/– Bevacizumab *vs*. TACE	PFS	Yes	600
NCT03419897 Rationale-208	Second line	II	Tislelizumab	ORR	No	249
NCT03062358 Keynote-394	Second line	III	Pembrolizumab *vs*. Placebo	OS	No	450
NCT03383458 Checkmate-9Dx	Adjuvant	III	Nivolumab *vs*. Placebo	RFS	Yes	530
NCT03867084 Keynote-937	Adjuvant	III	Pembrolizumab *vs*. Placebo	RFS, OS	Yes	950
NCT03847428 Emerald-2	Adjuvant	III	Durvalumab +/– Bevacizumab *vs*. Placebo	RFS	Yes	888
NCT04102098 Imbrave-050	Adjuvant	III	Atezolizumab+ Bevacizumab *vs*. Placebo	OS	Yes	662

pts, patients; aLLD, advanced liver limited disease; ORR, objective response rate; PFS, progression free survival; RFS, relapse free survival; OS, overall survival; NCT, Number of Clinical Trial (https://clinicaltrials.gov/).

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