Editorial Commentary

The TRIPLET study: more is better?

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Comment on: Zhang TQ, Geng ZJ, Zuo MX, *et al.* Camrelizumab (a PD-1 inhibitor) plus apatinib (an VEGFR-2 inhibitor) and hepatic artery infusion chemotherapy for hepatocellular carcinoma in Barcelona Clinic Liver Cancer stage C (TRIPLET): a phase II study. Signal Transduct Target Ther 2023;8:413.

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Hepatocellular carcinoma (HCC) remains one of the most common and most challenging cancers to treat. It arises on the background of chronic liver disease which may be both viral, hepatitis B and hepatitis C; or non-viral most commonly alcohol-related or metabolic associated liver disease (MASLD), previously referred to as non-alcoholic fatty liver disease (NAFLD). The observation that individuals with HCC often have underlying severe liver disease means that they tolerate therapy less well, and so balancing the beneficial effects of treatment with toxicity is frequently challenging. Furthermore, unless individuals with chronic liver disease are within a screening programme HCC often presents at advanced stages of disease. These two factors often preclude curative treatment by resection, ablation or transplantation.

HCC is divided into multiple stages as defined by the Barcelona Clinic Liver Cancer (BCLC) staging system (1). This classification correlates well with treatment options and outcomes. BCLC stage 0 (very early) or A (early) can be treated with curative surgical therapies or ablation, whereas stage B (intermediate stage) is suitable for transarterial chemotherapeutic embolization (TACE). In general, stage C (advanced stage) requires systemic therapy, and stage D (terminal stage) patients are suitable for palliative care only. The BCLC staging has been recently updated to reflect changes in clinical practise and the emergence of new therapeutic regimens (2).

HCC has been challenging to treat systemically. Chemotherapy agents have generally not been of benefit when given systemically, but agents such as FOLFOX (oxaliplatin, fluorouracil and leucovorin) can be useful when given via the hepatic artery (3). Currently the standard of care for systemic treatment of HCC include multi-tyrosine kinase inhibitors (TKIs), anti-programmed cell death protein ligand 1 (PD-L1) or programmed cell death protein 1 (PD-1) inhibitors, anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and anti-vascular endothelial growth factor (VEGF) therapies generally used in combination [reviewed in (4)]. The breakthrough in systemic HCC therapeutics for BCLC stage C was the SHARP trial published in 2008 which showed a 3-month improvement in median survival in unresectable HCC in individuals treated with the multi-kinase inhibitor sorafenib (5). This drug targets rapidly accelerated fibrosarcoma (RAF), VEGF and platelet-derived growth factor (PDGF) signalling pathways (6). Following the revolution in immunotherapy, this has been superseded by immune based therapeutic regimens. The first successful trial was atezolizumab (anti-PD-L1) and bevacizumab [anti-vascular endothelial growth factor alpha (VEGFA)] in the landmark IMbrave150 trial (7). This demonstrated improved survival in patients treated with this therapeutic combination compared to the then standard of care, sorafenib. In the atezolizumab/bevacizumab arm 82% of individual were in the BLCL-C stage, and objective responses by the modified response evaluation criteria in solid tumors (mRECIST) criteria were observed in 33.2%

individuals. This improved survival has been confirmed in a recent meta-analysis (8). Newer immunotherapy regimens involving different checkpoint inhibitors have emerged with similar efficacies. These trials include HIMALAYA, durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4) (9); and CARES-310, camrelizumab (anti-PD-1) and rivoceranib, also known as apatinib, a selective VEGFR2-targeted TKI (10). Conversely studies combining PD-1/PD-L1 blockade with TKIs have not shown benefit over TKIs alone, an example being LEAP002, which investigated the combination of pembrolizumab (anti-PD-1) and lenvatinib (TKI) (11). Therefore, despite these exciting advances in treatment of HCC and the ensuing options for individuals with BCLC stage C disease, the median survival remains around two years and so there remains an urgent need for new therapeutic regimens. These can be of two types: novel types of therapeutics or combinations of existing treatments (12).

The study of Zhang *et al.* takes the path of rational combination, by investigating the utility of camrelizumab and apatanib (rivoceranib) in combination with hepatic artery infusion chemotherapy (HAIC) using the FOLFOX regimen in a study called TRIPLET (13). This phase two study enrolled 35 patients with HCC arising on the background of chronic hepatitis B to receive up to six cycles of HAIC plus camrelizumab every 21 days and oral apatanib taken daily. HAIC was supplemented with embolization of branch arteries, and took up to 3 days to complete. Therapy was discontinued in the event of disease progression, toxicity, or death, but also if the tumours downstaged to a level where there was an opportunity to perform a curative treatment. The study group were followed up for a median duration of 23 months. Individuals had a median number of six HAIC cycles and nine camrelizumab cycles and the median duration of therapy with apatanib was 9.1 months. The objective response rate according to the mRECIST criteria was 88.6%, and this included the group of individuals with large tumours greater than 10 cm. Median progression free survival was 9.53 months. At 2 years the overall survival was 65%, and 6 of the 35 patients had their disease downstaged to a level such that they were able to receive curative therapy; five had resection and one had curative ablation. Not surprisingly this combination of treatments had a number of side effects, with treatment cessation required in four individuals. Seventy-four percent of patients had treatment related adverse events of grade three or above, with the commonest events being reduced neutrophil or lymphocyte counts. Grade 1 to 2 hypertension was noted in 40% individuals and this was most likely related to apatanib. Fourteen percent experienced a serious adverse event and 14% had immune-related side effects. There was also a transient reduction in quality of life and deterioration in liver function in some individuals. These are certainly encouraging results for patients with BCLC intermediate stage disease.

The patient group studied was representative of BCLC stage 3 individuals with 60% of the individuals having tumour sizes over 10 cm and over 70% having evidence of portal venous thrombosis. However, it should be noted that these individuals all had Childs Pugh A disease and the vast majority had a normal body mass index, with performance status of zero or one. Thus, although their disease was in the BCLC intermediate category their general health was good, which is often not the case in individuals with HCC, who are frequently ineligible for clinical trials. A recent pooled analysis of 288 patients treated with camrelizumab and TACE in BCLC stage C patients showed a complete response rate of 7.35%, a partial response rate of only 37.1% and progression free survival of 6.2 months (14). Thus, the study by Zhang *et al.* (13) compares favourably with historical data, especially with its partial response rate of 77.1%. Nevertheless the complete response rate in this study was similar to historical data at 11.4%.

There are some study limitations. The study population considers only individuals with chronic hepatitis B. This is reasonable considering the geographic location and the high incidence of HCC arising on the background of hepatitis B in China. However, this does not reflect the global nature of HCC, in which the more difficult to treat individuals are likely to come from the MASLD population. Whilst there is vaccination available to prevent hepatitis B infection the prevalence of MASLD associated HCC is increasing dramatically due to the global epidemic of obesity, and so these individuals should not be overlooked (15). The authors note that this is a phase two study and requires evaluation in a phase three clinical trial which they say is currently underway, and in which the TRIPLET combination is compared to dual therapy with camrelizumab and apatanib (NCT05313282). Currently it appears that individuals with MASLD-associated HCC respond less well to checkpoint inhibitors such as anti-PD-L1 or anti-PD-1, and therefore it may be difficult to extrapolate the findings of this study to this group of individuals (16). Nevertheless, the premise that combining a successful regimen of systemic therapy with a targeted approach, such has TACE, has merit.

Future treatment for HCC will be enhanced by

appropriate stratification of patient groups for therapy. This can be done on clinical grounds. For instance the TRIPLET regimen appears to have merit for individuals with HCC arising on the background of chronic hepatitis B. There has also been a suggestion that MASLD-associated HCC may respond better to tyrosine kinase inhibition, than checkpoint inhibitors (17). However, it is more likely that molecular stratification will ultimately be the way ahead for treating individuals with HCC, so that individualised therapeutic regimens can be prescribed. This will be important as even in this current study a substantial number of individuals had side effects. It should also be recognised that individuals volunteering for clinical trials are likely to be more enthusiastic about tolerating therapies in the face of adverse events, than unselected patients. One exciting molecular set of targets in HCC are the multiple signalling pathways that are disrupted in HCC. Within this the Wnt/β-catenin pathway is frequently constitutively activated (18). Thus, although generic TKIs are being used, there is a huge opportunity for this signalling pathway to be directly targeted, and such inhibitors are currently in phase one or two trials, as well as in preclinical development stages.

Despite the exciting opportunities for treatment for HCC, the challenge of toxicity with this and other current regimens for HCC remains. Simply combining therapeutics may not be the answer, as the improvement in efficacy will need to be carefully balanced against the downsides of toxicity. Holistic and individualised approaches are therefore likely to be the most successful opportunity. In the interim we await the results of the phase three study by this group, to see if it genuinely represents an improvement on the current optimal regimens of PD-1/PD-L1 blockade with anti-VEGF therapy.

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