Commentary

Hepatocellular carcinoma as the Rose of Jericho: from the desert of sorafenib, to the blossoming of immunotherapy

Antonio D'Alessio[1,2], Lorenza Rimassa[2,3]^

[1]Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, London, UK; [2]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [3]Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

Correspondence to: Lorenza Rimassa. Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve Emanuele, Milan, Italy; Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Email: lorenza.rimassa@hunimed.eu.

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According to its etymology, the English word "liver" is related to the verb "to live", and indeed there are few domains of oncology research as lively as liver cancer. The therapeutic landscape of hepatocellular carcinoma (HCC) has been rapidly changing over the last years, after the successful introduction of immune checkpoint inhibitors (ICIs) as standard of care for the treatment of unresectable or metastatic HCC (uHCC). Following more than a decade of tyrosine kinase inhibitors (TKIs) as the only available treatment for advanced HCC, in 2020 the results of the IMbrave150 trial radically changed the therapeutic algorithm (1,2). The combination of the anti-programmed death ligand 1 (PD-L1) monoclonal antibody (mAb) atezolizumab and the anti-vascular endothelial growth factor (VEGF) mAb bevacizumab outperformed sorafenib in terms of overall survival (OS) and progression-free survival (PFS), meeting both its co-primary endpoints. The combination has been recognised as the new first-line standard of care by all major scientific societies, and it has been approved by regulatory agencies worldwide (3).

With the rapid changes in this *lively* domain, the review by Zhang *et al.* comes as a timely and comprehensive publication (4). The authors put in perspective the recent results of the HIMALAYA and the COSMIC-312 trials, which will likely challenge the role of atezolizumab plus bevacizumab as the only immunotherapy treatment for first-line HCC. In particular, the HIMALAYA trial was a large phase III randomised trial, which proved the superiority of the combination of a single priming dose of tremelimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) mAb, and durvalumab, an anti-PD-L1 mAb (STRIDE regimen), against sorafenib, meeting its primary endpoint (5). After a median follow-up of 33.18 months, the combination achieved a median OS of 16.4 (95% CI: 14.2–19.6) months versus 13.8 (95% CI: 12.3–16.1) months with sorafenib [hazard ratio (HR) 0.78, (95% CI: 0.65–0.92); P=0.0035]. As also acknowledged by the latest update of the Barcelona Clinic Liver Cancer (BCLC) algorithm (6), these results establish the combination of durvalumab plus tremelimumab as a novel therapeutic option for treatment-naïve patients, alongside atezolizumab plus bevacizumab. On the other side, the COSMIC-312 trial (7) was another large, randomized phase III trial testing the combination of atezolizumab plus the oral TKI cabozantinib versus sorafenib and versus cabozantinib as single agent, with PFS and OS of the combination versus sorafenib being dual primary endpoints. However, despite a significant improvement of median PFS [6.8 (95% CI: 5.6–8.3) months versus 4.2 (95% CI: 2.8–7.0) months, HR 0.63, P=0.0012], the combination failed to demonstrate a significant

^ ORCID: 0000-0001-9957-3615.

advantage in OS.

Is PFS an adequate surrogate endpoint for OS? Zhang *et al.* (4) highlighted the potential biases embedded in the evaluation of OS, including subsequent treatments, short follow-up, and the survival plateau achieved by ICIs which is often not exhaustively captured by the median OS. However, most likely, a univocal answer does not exist. PFS could be considered a satisfying surrogate endpoint of OS only at certain conditions, for example with an HR less than 0.6 (8). Consistently, the advantage in PFS observed in COSMIC-312 did not translate into a concurrent improvement of median OS, making this combination a less appealing alternative for first-line treatment compared to atezolizumab plus bevacizumab and durvalumab plus tremelimumab.

Interestingly, the authors suggest the evaluation of objective response rate (ORR) as a potential surrogate endpoint. The combination of atezolizumab plus bevacizumab undoubtedly achieved an unprecedented ORR of 30% per RECIST criteria v1.1 in the updated analysis, which increased to 35% if assessed per modified RECIST criteria (2). ICIs are already under investigation in the perioperative setting as neoadjuvant treatment (9-12). The high rates of response could open completely new scenarios in the treatment of HCC, including the use of ICIs combinations as a downstaging strategy for unresectable patients.

The paper is highly provocative when addressing the issue of stage migration. A more integrated approach could be useful to increase the share of patients who could potentially benefit from curative, radical treatment, including liver transplant as envisioned by the groundbreaking study of Mazzaferro *et al.* (13). Also, considering the growing application of ICI combinations in the neoadjuvant setting, ORR could be increasingly used as a new clinically significant endpoint, alongside with further translational endpoints, such as the rate of major pathological responses (10).

Another interesting point touched by the authors includes the safety of the combination therapies. Despite the milestone achievements in terms of efficacy, the use of combination therapies involves the risk of an additive spectrum of toxicity. In particular, when using two agents from different pharmacological families, such as in the combination of atezolizumab and bevacizumab, patients can suffer from both immune-related and antiangiogenic-related adverse events, adding a further layer of complexity in the management of these novel treatments. Also, adverse events could be associated with improved survival, especially for immune-related events (14). Potential predictive biomarkers of toxicity could be crucial in identifying patients at increased risk, in particular for bevacizumab-related gastrointestinal bleeding events. At this regard, the authors suggest that real-life studies could provide precious evidence to inform clinical practice, and collaborating efforts are already shedding light on the subject (15).

Despite the steps forward made in the treatment of HCC, many questions still remain open. For instance, tumours harbouring certain molecular features, namely the hyperactivation of the WNT/β-catenin axis, could be primarily resistant to immunotherapy (16). For this reason, the identification of potential biomarkers of response to ICIs could give a decisive contribution to tailor the treatments for patients with HCC. Also, as the authors highlight, no valid treatment options are available upon PD-L1 acquired resistance, and robust, prospective data are eagerly awaited. The potential mechanisms leading to immune escape lie in the tumour microenvironment, which can dynamically change and contribute to resistance to ICIs. The intriguing proposal of a serial collection of biopsies during the treatment could be helpful to tackle the issue of immune evasion, and it could provide a longitudinal monitoring of biological changes induced by ICIs.

The therapeutic landscape portrayed by Zhang *et al.* (4) could further increase in complexity in the next future, with the upcoming reports from two major phase III ICI trials, as the CheckMate-9DW and the LEAP-002 (17). The authors were able to depict how clinical and translational research successfully managed to turn a traditionally treatment-deprived disease as uHCC into a rich therapeutic algorithm, with a positive impact on patients worldwide.

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