

Editorial

Novel Therapies for Hepatocellular Carcinoma

Lorenza Rimassa ^{1,2} 

¹ Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center-IRCCS, 20089 Rozzano (Milan), Italy; lorenza.rimassa@hunimed.eu

² Department of Biomedical Sciences, Humanitas University, 20090 Pieve Emanuele (Milan), Italy

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Since 2007, for patients with advanced- or intermediate-stage hepatocellular carcinoma (HCC) unsuitable for locoregional treatments and with preserved liver function, the multikinase inhibitor (MKI) sorafenib has been the worldwide standard of care [1,2]. After ten years of unsatisfactory results, additional agents with prevalent antiangiogenic activity have been approved based on positive phase 3 data: lenvatinib [3] in the first-line setting, regorafenib [4], cabozantinib [5], and ramucirumab [6] for patients previously treated with sorafenib.

Also, immune checkpoint inhibitors (ICI) targeting the programmed cell death receptor-1 (PD-1) as monotherapy or in combination with a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody have been granted accelerated approval in sorafenib-pretreated patients based on phase 1/2 data [7–9]. Although phase 3 trials testing ICI alone as first- and second-line therapy failed to meet their primary endpoints [10,11], based on the potential interplay between antiangiogenic drugs and immunotherapy, novel combinations of ICI plus antiangiogenics have been tested in untreated patients with encouraging preliminary results [12,13]. Moreover, other important early phase studies have tested molecular therapies directed against different novel targets, such as transforming growth factor-beta, MET (the hepatocyte growth factor receptor), and fibroblast growth factor receptor 4 [14].

Recently, the phase 3 IMbrave150 trial demonstrated the superiority of the combination of atezolizumab (a monoclonal antibody blocking the programmed cell death-ligand 1 [PD-L1]) plus bevacizumab (a monoclonal antibody against the vascular endothelial growth factor [VEGF]) compared to sorafenib in the front-line setting and established the new standard of care for these patients [15].

Further combinations of anti-PD-1/PD-L1 and MKI or anti-CTLA-4 and are being evaluated in phase 3 trials and might expand the therapeutic scenario in the next years [14,16–18].

However, an important unmet need is currently represented by the lack of clinical and/or biological factors and/or biomarkers that can guide therapeutic choices, apart from AFP, which is used to select patients for ramucirumab. This unmet need is being addressed in several studies that integrate translational research with the aim of better defining the biological tumor profile and identifying tumor and blood biomarkers to select patients who may really benefit from a specific therapy [14].

In this rapidly evolving scenario, it is extremely important that physicians are updated and aware of novel therapeutic options in order to make the best use of them in various clinical settings [19,20].

This Special Issue will highlight the key open issues and future perspectives for patients with advanced HCC, such as novel therapies and approaches, novel therapeutic targets, and biomarkers.

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