Editorial

Editorial comment on: "*Systemic treatment of hepatocellular carcinoma: an EASL position paper*"

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Hepatocellular carcinoma is the most common cancer of the liver and worldwide, the sixth most common cancer and the third most common cause of cancer related deaths (1). The management and treatment of this disease requires a multi-disciplinary approach, which is observed in the staging and classification. In 1999, the development of the Barcelona Clinic Liver Cancer (BCLC) classification system helped to guide the appropriate treatments based on stage. While patients with stage A disease would be candidates for locoregional treatment including surgical resection, liver transplantation or liver directed therapy, treatment in patients with intermediate (B) or advanced (C) stage disease would be palliative, where the recommendation would for systemic therapy. For nearly a decade, sorafenib remained the only treatment option in patients with advanced hepatocellular carcinoma (2). Over the past several years, the treatment landscape has rapidly changed with the approval of several therapeutic agents in both the front-line and refractory setting for the treatment of hepatocellular carcinoma (3). Coinciding with these approvals, a continued improvement in overall survival has been observed from the initial 10.7 months seen in the SHARP trial to 19.3 months from the combination of atezolizumab and bevacizumab (2,4). In this recent published review article, Bruix *et al.* provide a comprehensive review of the systemic therapies available for advanced hepatocellular carcinoma. The authors recommend that the preferred treatment option in the front-line setting is the combination of atezolizumab/bevacizumab, while acknowledging the lack of data to guide which of the various treatment options should be used in the second line and beyond. The authors highlight several retrospective studies that examined the sequencing of various tyrosine kinase inhibitors after the progression of either sorafenib or lenvatinib and suggest that this may provide guidance at sequencing strategies for patients who receive these tyrosine kinase inhibitors. Due to the paucity of supporting data to guide treatment after atezolizumab/bevacizumab including the absence of predictive biomarkers to personalize treatment, there is no consensus of sequencing treatment after atezolizumab/bevacizumab. The approval of cabozantinib, regorafenib and ramucirumab (for patients with an AFP ≥400) were all in the setting of a prior sorafenib exposure and not examined in the setting of treatment from prior lenvatinib or atezolizumab/bevacizumab (3,5,6). Proponents for a "one size fits all" argue that the clinical efficacy observed from lenvatinib and sorafenib in the front-line setting would translate a similar benefit in patients with treatment refractory disease and be appropriate after atezolizumab/bevacizumab (2,7). However, there is no evidence to support this rationale and should not be considered as standard therapies in the second-line setting (8). Despite the lack of consensus to guide treatment in the second line setting in advanced hepatocellular carcinoma, one consideration when deciding which treatment includes the mechanism of action of the various therapeutic options. Whereas lenvatinib and sorafenib are potent anti-angiogenic agents that inhibit vascular endothelial growth factor (VEGF) similar to bevacizumab, several therapies that have demonstrated activity in the refractory setting also inhibit alternate signaling pathways associated with tumorigenesis in hepatocellular carcinoma. Preclinical studies have demonstrated upregulation of the

MET and AXL receptors as a mechanism of resistance to anti-angiogenic therapy. The suppression of MET and AXL using cabozantinib, a multi-targeted tyrosine kinase inhibitor with activity against the MET/AXL axis (9), impaired angiogenic treatment induced pro-metastatic activity and rescue from acquired treatment resistance (10). Additionally, the use of pembrolizumab would unlikely confer a significant clinical benefit after atezolizumab.

Whereas therapeutic options in the refractory setting have become more readily available and add to the complexity in the treatment landscape in the second-line setting, a similar conundrum will be observed for patients with treatment naïve advanced hepatocellular carcinoma. HIMALAYA, a randomized phase 3 trial that investigated the combination of durvalumab and tremelimumab compared to sorafenib, was recently announced as reaching its primary endpoint of overall survival (NCT03298451). The study included secondary endpoints of progression free survival, objective response rate and disease control rate. At this time, the results and data have not been released. Two additional ongoing phase 3 trials, LEAP-002 and COSMIC-312, are expected to be resulted in the near future (11,12). A press release from COSMIC-312 stated that one of the co-primary endpoint of progression free survival demonstrated a significant improvement at the planned primary analysis, whereas the co-primary endpoint of overall survival did not reach statistical significance. The data from the results have not been presented. If these two studies are deemed positive, this will further add to the complexity in the treatment in advanced hepatocellular carcinoma. In addition to scrutinizing the clinical efficacy across these various front line clinical trials, another consideration is comparing the treatment related adverse events. The patient population was limited to patients with Child-Pugh A disease, whereas a real-world patient population would include those with early stage Child-Pugh B disease that would otherwise be candidates for treatment but at increased risk for various treatment associated side effects.

The advancements in systemic therapies have drastically changed the treatment paradigm in hepatocellular carcinoma. While the emergence of new treatments has provided patients with more options, a continued debate remains in the sequencing of the various treatments. While there remains no data to guide treatment across various lines of therapies, for eligible patients, the *de facto* first-line therapy is atezolizumab/bevacizumab. At the time of disease progression or treatment intolerance, treatment strategies should include targeting alternate mechanisms of action from various therapies, where either regorafenib or cabozantinib would be the preferred treatment options in the second-line setting. Pending studies may add to further the treatment armamentarium while adding further complexity to the treatment landscape in advanced hepatocellular carcinoma.

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