Editorial

Cabozantinib and the moving field of systemic treatments in advanced hepatocellular carcinoma

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Most of patients with hepatocellular carcinoma (HCC), are diagnosed at an advanced-stage explaining the poor prognosis of this cancer with a median survival without treatment around 8 months (1-3). Currently, two systemic multi-kinase inhibitors with anti-proliferative and antiangiogenic effects are available as first line treatments in advanced HCC. The first one, Sorafenib, was the only available systemic treatment available during one decade and was associated with an improvement of overall survival of around 3 months compared to placebo (4,5). The second one, lenvatinib, showed a similar median overall survival compared to Sorafenib in a non-inferiority phase-3 trial (6). No second line was available during several years due to toxicity or absence of efficacy of the different drugs tested in multicentric phase 3 randomized controlled trials.

In 2017, regorafenib was finally approved in second-line in patients who tolerated but progressed under sorafenib and demonstrated an increase of overall survival (10.6 months) *vs.* placebo (7.8 months) (HR =0.63, 95% CI: 0.50–0.76; one-sided P<0.001). Compared to sorafenib, similar adverse events were observed (67% of grade 3 or 4 *vs.* 39% under placebo) (7). Recently, the results of the phase 3 randomized controlled CELESTIAL trial were published by Abou-Alfa *et al.* in *New England Journal Medicine* (8). This trial evaluated cabozantinib, a multi-kinase inhibitor (targeting VEGF, AXL and MET), compared to placebo in patients with advanced HCC previously treated by sorafenib. In this trial, 707 patients Child Pugh A from 19 different countries were randomized in a 2:1 ratio to receive either cabozantinib 60 mg (470 patients) or placebo (237 patients) stratified according to etiology, geographic region, extrahepatic metastasis and macrovascular invasion. All patients were previously treated with Sorafenib and had disease progression after at least one systemic treatment. Overall survival, the primary endpoint, were respectively 10.2 months in the cabozantinib and 8.0 months in the placebo group (HR =0.76, 95% CI: 0.63–0.92; P=0.005). Median progression-free survival was 5.2 months with cabozantinib and 1.9 months with placebo (HR for disease progression or death =0.44; 95% CI: 0.36–0.52; P<0.001). Sixty-eight percent of patients in the cabozantinib group presented grade 3 or 4 adverse events (*vs.* 36% in the placebo group) leading to a dose reduction in the majority of the patients and discontinuation of treatment in 16% of patients. The most frequent adverse events were palmar-plantar erythrodysesthesia (17% with cabozantinib *vs.* 0% with placebo), hypertension (16% *vs.* 2%), increased aspartate aminotransferase level (12% *vs.* 7%), fatigue (10% *vs.* 4%), and diarrhea (10% *vs.* 2%), similar to the adverse events observed with others tyrosine kinase inhibitors in HCC such as lenvatinib, sorafenib or regorafenib. In contrast to the regorafenib trial where no patients treated in third line were included, 27% of patients in the CELESTIAL trial were in third line of systemic treatments (8). However, the low number of patients treated by cabozantinib in third line and the absence of benefit of cabozantinib in this subgroup

of patients (HR =0.90, 95% CI: 0.63–1.29) preclude the use of cabozantinib as the reference arm in clinical trial testing new drugs in third line where placebo should still remain the comparator.

The field of systemic treatments of HCC is rapidly moving. Nivolumab, a monoclonal antibody against programmed-cell-death protein (PD-1), was also approved by the US Food and Drug Administration (FDA) based on the results of an open label non-comparative phase 1–2 study reporting a median overall survival of 15 months and a median duration of response of 9.9 months (9). Moreover, a recent report in ASCO meeting showed that ramucirumab (monoclonal antibody targeting VEGF receptor 2) increased slightly overall survival compared to placebo (8.5 *vs.* 7.3 months, HR =0.71, 95% CI: 0.531–0.949; P=0.0199) in second line in patients with advanced HCC and an AFP level ≥400 ng/mL (10).

Overall, the increasing armentorium of drugs available for advanced stages also increased the uncertainty about the sequence of systemic treatment that could be proposed for these patients. Currently, no strong recommendations could be done about how to choose between sorafenib and lenvatinib in first line. Even if lenvatinib is associated with more radiological response and prolonged progression free survival than sorafenib, these results were not translated in an increased overall survival. Regarding second line treatments, regorafenib could be used in patients who tolerated and progressed under sorafenib. Nevertheless, a useful impact of regorafenib after intolerance on sorafenib remain unknown and cabozantinib appears as a good strategy in this population of patients. Moreover, the results of the sequence of lenvatinib followed by regorafenib or cabozantinib is currently unknown because only patients treated by sorafenib in first line were included in second line randomized controlled trials. More data on cost/effectiveness will be also helpful to choose the sequence of treatment in the first- and second-line setting. The spectrum of adverse events should be also taken into account because monoclonal antibody as nivolumab or ramucirumab have less frequent adverse events than tyrosine kinase inhibitors such as sorafenib, lenvatinib or regorafenib. However, currently, nivolumab is not approved in Europe waiting the final results of the phase 3 against placebo and we are still waiting for the final publication of the ramucirumab trial. Finally, tumor biopsy will help to study tumor heterogeneity and tumor cell plasticity in order to better understand the mechanism of primary and secondary resistance to targeted therapy. Identification of tumor biomarkers predictive of response to a specific biotherapy will be useful to propose the most appropriate treatment in first and second lines. To reach this goal, a mandatory recent tumor biopsy should be required at the inclusion of patients in clinical trial testing new systemic therapy in patients with advanced HCC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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