

Donafenib in Chinese patients with advanced hepatocellular carcinoma (HCC): Really a new standard of care, or should we change paradigm for drug development in HCC?

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Liver cancer is the sixth most common cancer worldwide,¹ with over half of the new cases and death occurring in China. Hepatocellular carcinoma (HCC) accounts for 75-85% of primary liver cancers. Most patients are diagnosed at an advanced stage with poor survival rates;¹ thus, the diagnosis and treatment of HCC is a main public health concern, especially in China.

Donafenib is a novel oral small-molecule inhibitor of multiple tyrosine kinases, such as vascular endothelial growth factor receptors, platelet-derived growth factor receptor, and Raf kinases, thereby blocking both angiogenesis and tumor cell proliferation.² Donafenib is a derivative of sorafenib with a trideuterated N-methyl group, that may improve molecular stability and enhance the pharmacokinetic features.² Preclinical, phase Ia and Ib trials have shown favorable efficacy and safety profile.^{2,3}

Qin *et al.*⁴ recently reported in the *Journal of Clinical Oncology* the results from an open-label, randomized phase II-III trial, in which donafenib was compared with sorafenib, as first-line therapy in Chinese patients with unresectable or metastatic HCC. The trial showed the superiority of donafenib over sorafenib in increasing overall survival (OS) and thus the authors propose donafenib as 'new frontline standard for Chinese patients with advanced HCC'.

Is this statement correct? Probably yes... Is this true also for non-Asian patients? Probably no... But, more importantly, which are the most relevant considerations we can draw from this study (and all the other first-line trials available)?

Despite the significant OS advantage observed (median OS:

12.1 vs 10.3 months; HR: 0.831; 95% CI: 0.699 to 0.988; P=0.0245), patients enrolled in the donafenib trial clearly differed from those enrolled in other globally-conducted first-line pivotal trials.^{5,6} Indeed, although no differences were observed between treatment arms in terms of BCLC C stage, Child-Pugh score, and percentage of patients presenting with high AFP level, >90% of the enrolled patients were HBV positive, a well-known negative prognostic factor; furthermore, patients were also younger, median age being 53 years in both study arms, while it was constantly over 60 years (often well above this figure) in the sorafenib SHARP trial,⁵ the lenvatinib REFLECT trial,⁶ and the atezolizumab plus bevacizumab IMbrave 150 trial,⁷ this latter study having shown a significant OS advantage (again over sorafenib) in all main patients' subgroups, including HBV-positive and Asian patients.⁷

Once again, in our opinion, '... the issue is not the right drug [or combination], but the right patient'.⁸

Having, for the first time, at least three different options for the medical treatment of HCC patients, our choice should rely on more thorough biological and etiopathogenic considerations.

Possibly, donafenib could be the treatment option of choice in HBV-infected patients, a population which is more and more uncommon in western country, where the growing incidence of nonalcoholic fatty liver disease, now a recognized inflammatory disease,⁹ could theoretically benefit more from an immunotherapy-containing regimen; whether bevacizumab or lenvatinib is the best drug to combine with immunotherapy remains to be proven. Recent studies have indeed clearly demonstrated the immunomodulatory activity of lenvatinib,¹⁰ suggesting potential synergism with immune checkpoint inhibitors. Furthermore, the combination of lenvatinib with the anti-PD-1 antibody pembrolizumab yielded impressive results not only in kidney cancer,¹¹ but also in HCC, with a 46% objective response rate (95% CI, 36.0% to 56.3%), a 9.3-month median progression-free survival, and a 22-month median OS of 22 months, per mRECIST, within a phase Ib study.¹²

In our opinion, these considerations and hypotheses should be taken into account when designing the new generation of trials in HCC.

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