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LETTER TO THE EDITORS

# Reply to: Time to resize the role of everolimus as treatment of hepatocellular carcinoma recurrence after liver transplant

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Dear Sirs,

We thank Drs Mancuso and Perricone for their comments on our systematic review in Transplant International [1], which is the first systematic analysis comparing mammalian target of rapamycin inhibitors (mTORi) (including both sirolimus and everolimus) and calcineurin inhibitors (CNIs) with evaluation of particular characteristics associated with HCC recurrence after liver transplantation (LT) [2]. The authors in their letter emphasized that mTORi have no proven anticancer attitude for HCC treatment based on a recently published randomized controlled trial (EVOLVE-1) [3]. However, we have to mention that the latter study was performed in patients with advanced HCC after failure of sorafenib, that is, a completely different setting, compared to our systematic review, in which we evaluated the impact of mTORi on prevention of HCC recurrence after LT and not the treatment of recurrent HCC [2]. Hence, evaluating 3666 HCC liver transplant recipients from 42 studies, we found that HCC recurrence developed significantly more frequently in patients on CNIs than in patients on mTORi (13.8% vs. 8%, $P < 0.001$), although the former group of patients had more favorable HCC characteristics regarding Milan criteria and microvascular invasion. In addition, we found that post-LT HCC recurrence was significantly more frequently observed in patients who received sirolimus than in those who received everolimus (10.5% vs. 4.1%, $P = 0.02$), but this may be due to the more favorable prognostic factors of everolimus group. Nevertheless, although our systematic review [2] represents the best level of evidence for now in this setting, large well-designed studies are needed for stronger conclusions.

Finally, the authors mentioned that mTORi co-administration with sorafenib for HCC recurrent after LT has been associated with severe complications, such as fatal bleeding, possibly due to everolimus and sorafenib interaction. In fact, the authors referred to their previous publication including seven patients with recurrent HCC post-LT who received everolimus plus sorafenib [4]. In this cohort, 1 (14%) of the seven patients had hemorrhagic gastropathy leading to death. However, in another larger cohort [5], only 1 (3%) of the 31 recurrent HCC under everolimus plus sorafenib had fatal gastrointestinal bleeding. This discrepancy may be related to the different initial dosage of sorafenib which was used (800 mg/day vs. 400 mg/day in most of the patients, respectively). In addition, no data regarding the serum levels of mTORi were given in the former study [4], but the patient who had fatal hemorrhagic gastropathy was under relatively high dose of everolimus (3.5 mg/day) and sorafenib (800 mg/day) [4]. Nevertheless, we agree that this combination should be used with caution and again larger well-designed studies are needed for final conclusions.

In conclusion, although our systematic review evaluated the impact of mTORi on prevention of HCC recurrence post-LT, we believe that more studies are needed to confirm or not the futility of mTORi (and/or sorafenib) in the concept of 'personalized' treatment of recurrent HCC after LT [6].

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## Conflict of interest

Evangelos Cholongitas: invited speaker for BMS, Gilead, Novartis; Patrizia Burra: nothing to disclosure.

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