according to the BCLC staging classification, so this information is always available anyways. We also agree that the greatest weight in the ART-score is put on the aspartate aminotransferase (AST) and not on radiologic response. But this was derived from the hazard ratio in the multivariate analysis giving the greatest weight to the rising AST as opposed to other statistically significant parameters.

We acknowledge that the authors developed the HAP score [3], but the HAP score serves a different purpose: it is a prognostic score, which helps to subclassify BCLC-stage B patients undergoing chemoembolization into different prognostic groups prior the first TACE treatment. In contrast, the ART-score, aims to detect (1) patients that can tolerate repeated-TACE well and (2) patients, whose liver function and prognosis would be harmed by another occlusion of the arterial blood supply to parts of the liver. So patients might be in a good prognostic group by the HAP score or by the BCLC stage B subclassification at baseline, but a subgroup of these patients may present with an ART of $\geqslant$2.5 points prior to TACE-2 with subsequent dismal prognosis in case of retreatment with TACE. On the other hand, some suboptimal candidates for TACE at baseline may tolerate repeated TACE quite well as outlined by an ART score of 0–1.5 points and therefore have a fairly good outcome with TACE treatment, as detailed in our original ART-score manuscript.

Regarding the comments by Han and colleagues we would like to confirm that even if a patient receives 2.5 points in the ART-score through lack of radiologic response and an increase in CPS by 1 point after TACE 1, he still is a poor candidate for further TACE's. It might be true that he might show a radiologic response after the second TACE but this will lead to further deterioration in his liver function and therefore a dismal prognosis despite radiologic response. This has been clearly shown in our initial art score manuscript. Therefore the recommendations by different authors that patients should undergo at least two TACE-procedures initially – statements made well before the publication of the art score – cannot be supported anymore.

Regarding the impact of different TACE or TAE techniques, the authors misunderstood the message we are giving: it might be true that treatment with DC-beads gives a better treatment respond than cTACE (even though not supported by the published literature so far [4]), but this will be taken into account by the ART-score anyway through the parameter "radiologic response". Thus, different TACE techniques could have an impact on the ART-sore values; but nevertheless, the ART-score values obtained retain their prognostic significance regardless of the technique used.

We disagree with the authors that the response definition is different because we did not evaluate patients with complete response in our initial ART-score manuscript: the definition was the same but the inclusion criteria did not allow inclusion of patients with less than 2 TACE-procedures (which was obviously necessary to evaluate the impact of repeated TACE's on outcome, since patients with complete response do not receive retreatment with TACE within three months if TACE is applied in a "on demand" fashion). Patients that had a complete response after TACE 2 or TACE 3 did not receive further TACE sessions in our institutions, as outlined very clearly in the methods of our manuscripts. So the validation of the ART-score seems to be very robust but we certainly welcome further evaluation of the ART-score in different patient populations worldwide, in particular when performed prospectively.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Triple or dual therapy for HCV-1 naive patients? Optimizing selection tools

To the Editor:
We read with interest the paper by Andriulli *et al.* [1] about the identification of naïve HCV-1 patients who can be treated with dual therapy according to baseline and on-treatment parameters. Important predictive factors of sustained virological response (SVR) are the *IL28B* single-nucleotide polymorphisms (SNPs), however the authors considered only the rs12979860 SNP, forgetting the more important rs8099917 [2–4]; this is, in our opin-

ion, not just an academic discussion, because the role of rs8099917 has been clarified and deepened in several studies and we think it should be included as best SVR predictor in the genotype 1 [2–4]. The major impact of rs12979860 has been documented on the early response [5], while rs8099917 in a recent meta-analysis evidenced the best predictive effect on the SVR (OR = 5.171 *vs.* 4.473) [6]. In fact, the effect of this SNP explains the higher rate of relapse in patients who achieved both RVR and ETR with the CC rs12979860 genotype, but with the presence of a G allele for the rs8099917 SNP [5]. Conversely, patients without the CC genotype for rs12979860 retain good probability to reach SVR if they have the TT genotype for rs8099917; this issue could underlie the high rate of SVR in non-CC patients reported by Andriulli *et al.* [1] and according with the TT prevalence in the Italian population. Therefore, we consider it essential to get both rs12979860 and rs8099917 SNPs as predictors on SVR and, in more detail, we could select the patients with CC/TT or CT/TT, but not with CC/TG or CC/GG genotype, for dual therapy.

Another not considered issue in the analysis is the role of therapeutic drug monitoring (TDM) of ribavirin (RBV) as useful early on treatment predictor of response and toxicity. Ribavirin shows a wide inter-individual variability in plasma concentrations (~25–30%) and weight-based dose results often inadequate without TDM support [3,4,7]. Interestingly, RBV concentrations are related both with EVR and SVR [3,4,8,9] or treatment failure in HCV-1 infected patients, according to different plasma concentrations at different time-points. The optimal therapeutic range of RBV could maximize the SVR achievement and it should be comprised between 2–2.5 mg/L (at week 4 of therapy), according to the majority of the reviewed studies [10].

In conclusion, we suggest that both *IL28B* SNPs should be considered in order to refine the selection of candidate patients for dual therapy and then the TDM of RBV should be used to improve the on-treatment management.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to "Triple or dual therapy for HCV-1 naive patients? Optimizing selection tools"

To the Editor:

We thank Dr. Boglione and colleagues [1] for their comments on our recently published paper on the identification of naïve HCV-1 patients with chronic hepatitis who may benefit from dual therapy with peg-interferon (PegIFN) and ribavirin (RBV) [2]. To date, several single nucleotide polymorphisms (SNPs) in the genes encoding for IFN-λ1 (*IL29*), IFN-λ2 (*IL28A*), IFN-λ3 (*IL28B*), and IFN-λ4 (*IFNL4*) have been established as predictors of treatment response to PegIFN/RBV [3,4]. Among the identified SNPs, rs8099917, rs12979860, and the newly ss469415590 polymorphisms have been extensively investigated. Although with conflicting results, the question about which of the aforementioned SNPs, alone or in combination, is (or are) the best baseline marker(s) of SVR in patients HCV1 is still debated.

Dr. Boglione *et al.* argue that the contemporary evaluation of the two SNPs of the *IL28B* locus may portend greater information