Editorial

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Progression-free survival: Starting point or endpoint in advanced HCC trial design?

Richard S. Finn*

Department of Hematology/Oncology, Geffen School of Medicine at UCLA, Los Angeles, California, United States

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In the current issue of the *Journal* we are presented with a thoughtful perspective on drug development in advanced hepatocellular carcinoma (HCC).[1] The authors apply their extensive experience in HCC to review the current data supporting the numerous successes in phase III HCC drug development (regorafenib, lenvatinib, cabozantinib, ramucirumab) as well as reasons for the ~15 failures since the initial approval of sorafenib in 2007. The over interpretation of single arm phase II studies, lack of patient enrichment strategies, and drug toxicity are all correctly identified. Not mentioned is a greater appreciation for other important prognostic factors in HCC such as an elevated alpha-fetoprotein (AFP), separating extrahepatic spread from microvascular invasion, and the site of progression.[2] The first 2 have already been accounted for in stratification schemes in completed studies and are included in ongoing studies.[3] However, site of progression is yet to be assessed in a prospective randomized study as a stratification factor.

The provocative part of this paper is the suggestion that progression-free survival (PFS) is an appropriate endpoint in trials of advanced HCC. To support their claim, the authors performed a meta-analysis of available trial data to suggest that a hazard ratio (HR) for PFS of <0.6 should correlate with a statistically significant improvement in overall survival (OS) and therefore could be used as a primary endpoint in prospective trials of HCC. The largest limitation of this study is that it is not based on individual patient data but rather the data reported in manuscripts for the entire trial population, which does not account for potential confounding factors. Other limitations are the inconsistent reporting of all endpoints [*i.e.* PFS and not time to tumor progression, or vice versa] as well as inconsistent use of response assessments (RECIST *vs.* mRECIST). Perhaps the biggest practical weakness of the study is that the area in drug development in HCC where PFS would be most useful as a surrogate endpoint in trial design is in the front-line setting, where survival times are becoming longer. The authors recognize that their analysis "is supported mainly by positive trials in the second-line setting comparing active drugs *vs.* placebo" and therefore recommendation in the front-line setting "should be tempered due to the lack of confirmatory data."

The end-goal of all of our research activities is to improve clinical benefit for patients. OS is the gold standard for demonstrating clinical benefit.[4] It is defined as the time from randomization to death and is not subjective like radiology-based endpoints. To date, this has been the endpoint of choice in HCC trials in both the front-line and second-line setting. The fact that we are now discussing PFS as an endpoint shows a significant evolution in our thought process in HCC since 2007.[5] In addition, the Food and Drug Administration has recently posted that PFS would be accepted as potential endpoint in HCC trials.[6] In the United States, we currently have 6 approved drugs for the treatment of HCC: in the front-line setting sorafenib and lenvatinib, and in the second-line setting regorafenib and cabozantib and both nivolumab and pembrolizumab based on accelerated approval mechanisms. Approval of ramucirumab in the AFP ≥400 ng/ml population is expected based on positive phase III data.[7] With this rapid change in the landscape, almost all of the phase III studies in HCC are aimed at the front-line setting. Most likely, the last placebo controlled study in second-line to be performed is the KEYNOTE-240 study of pembrolizumab *vs.* placebo (NCT NCT02702401) which recently reported a negative result.[8] While the data has not been presented, this study aimed at improving OS, and could have been impacted by the use of newly approved drugs at progression on study. Given that second-line studies will no longer be placebo controlled, the relevance of PFS *vs.* an active control may not hold up as in the analysis performed in the current paper. With this in mind, the natural history of advanced HCC is likely changing with the availability of more active drugs, which will make *proving* an intervention improves OS much more difficult even though we may see a significant improvement in PFS.

This point is especially relevant in the front-line setting. One of the advantages of a surrogate endpoint such as PFS is that in a disease that has a longer survival such as advanced hormone-receptor positive breast cancer, (median OS of 3–4 years) it could take years before a new effective drug is made available to patients if OS was the standard for approval, which would be unacceptable. This burden is not only on regulators to accept these endpoints but also on payers, who often refuse to reimburse for surrogate endpoints denying access of potentially life extending drugs to patients in need. Historically, HCC did not fulfill these criteria as OS was still under a year in front-line

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* Corresponding author. Address: Department of Hematology/Oncology, Geffen School of Medicine at UCLA, Los Angeles, California, United States. Tel.: +1 310 586 2091; fax: +1 310 586 6830.
E-mail address: rfinn@mednet.ucla.edu.

studies but now there is increasing evidence that survival for subsets of patients may be 2 years or more.[9,10] This could very well become even longer as there are now several drugs that are proven active in advanced HCC. In sequence, these agents may have a cumulative effect on OS moving forward.

In a clinical study, OS is a function of not only PFS of the interventions being studied but survival post-progression (SPP) as well. In a pivotal study, Broglio and Berry examined the impact of SPP on detecting the treatment effect on OS.[11] They carried out statistical simulation studies under the assumption that PFS differed between treatment arms while SPP was the same. The simulation studies found that there was no statistically significant difference in OS because of the dilution effect from SPP, although there was a statistically significant difference in PFS between treatment arms. This leads them to conclude that "OS is a reasonable primary endpoint when median SPP is short but is too high a bar when median SPP is long, such as longer than 12 months". When there were no active drugs beyond sorafenib, HCC probably would have met this criteria, but with the advent of second-line agents this is likely changing. Applying this to HCC where conservatively we will estimate that SPP is about 10–12 months after sorafenib or lenvatinib in the front-line setting, for a study to have 90% power to detect a significant difference in OS, we are looking at study of 1,300–1,500 patients (Fig. 1). This is very different from the studies we have performed to date. Indeed, if OS continues to be the only primary endpoint accepted, the approval of new drugs will likely be delayed, leaving active drugs on the shelf. Therefore, it would seem that the time has come to accept PFS as a primary endpoint in front-line trials in HCC, as long as it meets some minimal threshold, either the HR <0.6 proposed by the authors or perhaps some absolute number (*i.e.* 6 months or more). Even in breast cancer where new drugs have demonstrated more than a 10-month improvement in PFS (HR = 0.58; 95% CI 0.46–0.72; p <0.001) studies are not adequately powered to demonstrate a significant improvement in OS because of SPP.[12] This leads us to the unsatisfying conclusion that just because a study does not demonstrate a statistical improvement in OS does not mean there is no benefit on OS.

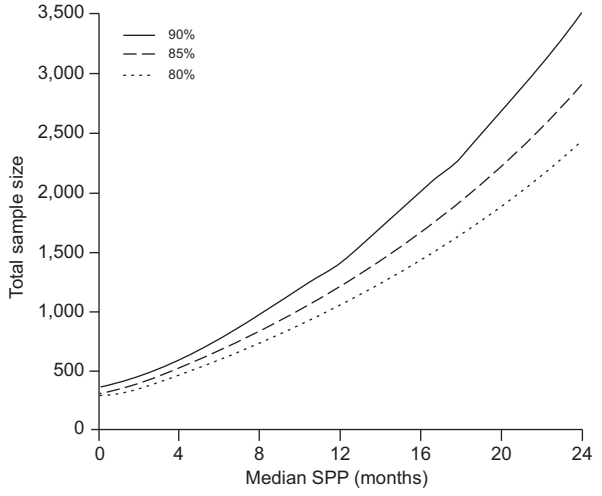

Fig. 1. Probability of statistically significant differences in overall survival as a function of median survival post-progression. The 3 curves were indexed by the power for detecting the actual median progression-free survival benefit that was simulated, 6 *vs.* 9 months (*i.e.*, powers of 90%, 85%, and 80%). Figure reused from[11] with permission. SPP, survival post-progression.

Moving ahead, more efforts to identify patients most likely to benefit, either based on clinical characteristics or biomarkers, would make achieving meaningful improvements in OS easier. This is especially challenging in the case of checkpoint inhibitors, where patients that respond have an exceptionally long duration of response but cannot, at this point, be selected for prospectively. This fact alone is the largest risk factor for the success of this approach in HCC. In addition, with regards to PFS, it has been suggested that PFS may not capture the full benefit of this class of drugs, which seem to elevate the tail of the survival curve.[13]

In conclusion, the authors should be congratulated for their effort and for formally raising the question of PFS as an endpoint in HCC in this publication. Personally, given the issues with SPP, I would agree that it is time to start using PFS as a primary endpoint in HCC studies in the front-line setting and probably second-line setting as well. Given that we will likely soon see drugs developed in the third-line and beyond, OS will likely stay the standard in those settings. At this time with so many completed phase III studies in HCC, a meta-analysis using individual patient data is justified to better evaluate if PFS is a valid surrogate for OS. Given the effort by patients, research staff, and clinicians to drive accrual of these phase III studies, and the subsequent revenue to industry provided by their efforts, sharing these data for this purpose should be demanded, and if not provided, a legitimate explanation by sponsors needs to be made public.

Conflict of interest

RSF has received consulting fees from AstraZaeneca, Bayer, Bristol Myers Squibb, Esiai, Exilixis, Eli Lilly, Novartis, Merck, Pfizer, Roche/Genentech.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.03.002.

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