Editorial

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Trial endpoints for systemic therapy in patients with hepatocellular carcinoma

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It is over 10 years since an international expert panel published guidelines for the design and choice of endpoints for clinical trials in hepatocellular carcinoma (HCC).[1] That same year, 2008, the seminal SHARP trial was published, providing unequivocal evidence that sorafenib improves survival in advanced disease.[2] A standard-of-care was established and some principles of trial design were defined. Perhaps the most important of which was the selection of patients with well-compensated liver disease as defined by the Child-Pugh A classification. Subsequent field of practice studies have demonstrated very poor survival in patients with Child-Pugh B and C disease treated with sorafenib, underlining the critical importance of liver function in patient selection.[3] In fact, the selection of patients with well-compensated liver disease obviated the concerns expressed in the guideline that competing risk of death due to chronic liver disease would confound progression free survival (PFS) as an endpoint. For phase II trials, time to progression (TTP), as defined by radiological progression, was recommended in favour of PFS, which is a composite endpoint defined by both progression and death. Overall survival (OS) was recommended as the appropriate endpoint for phase III trials. In the intervening years there have been a large number of clinical trials performed in advanced disease and, while many have been negative, the past 2 years have seen significant progress leading to Food and Drug Administration (FDA) approval of 5 new drugs. Four of these are second-line agents and the OS for those receiving a sequence of 2 active agents is over 2 years.[4]

The wealth of data accrued from these trials provides an opportunity to re-evaluate trial design and the review by Llovet and colleagues is both timely and welcome. A key issue, and one that has been faced in other tumour types, is the appropriate endpoint for phase III trials. Whilst OS is robust and clinically meaningful, it requires large trials with long follow-up, and can be confounded by crossover or post-progression therapy. The use of surrogate endpoints has the potential to overcome these limitations but requires careful validation. The proposed surrogate should correlate strongly and consistently with the definitive endpoint and should predict the net effect on clinical outcome. However, the role of PFS as a surrogate has been shown to vary with tumour type, class of drug and line of therapy such that evaluation in the setting of HCC is warranted.[5] The study by Llovet *et al.* analysed trial-level data from 21 randomised, phase III, systemic therapy trials of which 12 are first-line and 9 second-line. The primary endpoint for all studies was OS which was met by 2 first-line and 3 second-line trials. PFS was a secondary endpoint in 16, TTP in 16, and 11 reported both PFS and TTP. The correlation between PFS and TTP was extremely high ($R = 0.99$) and both PFS and TTP had a moderate correlation with OS ($R = 0.84$ and 0.83, respectively). For PFS, a threshold hazard ratio (HR) of ≤0.6 was proposed as a minimum surrogate to predict survival. According to the linear regression equation, a PFS HR of 0.6 is predicted to result in an OS HR of 0.83. Understanding the correlation between PFS and OS is certainly informative but there are some limitations that demand caution before PFS can be broadly adopted. First, the proportion of positive trials was low, and only 3 of the 5 positive trials reported PFS; all 3 were second-line trials. PFS was not reported for the first-line SHARP and Asia Pacific trials but has been estimated using TTP based on the close correlation between TTP and PFS. Second, the REFLECT trial met its primary endpoint for non-inferiority with respect to OS and the role of PFS as a surrogate for this endpoint is not clear. Finally, all trials to date have evaluated tyrosine kinase inhibitors and the performance of PFS as a surrogate for OS in trials of immunotherapy is yet to be determined. Recent analyses of randomised trials of immunotherapy have demonstrated a weak correlation between PFS and OS.[6,7] The results of first- and second-line randomised trials of nivolumab and pembrolizumab in HCC are eagerly awaited and will provide informative data on the utility of PFS as a surrogate in this setting.

Successful FDA approval is often implied to be an indicator of a 'positive' or successful trial outcome and indeed this may, from a commercial viewpoint, be true but the clinical community should remain cautious.[8] A recent analysis shows that of all 71 FDA anti-cancer drugs approved by the FDA between

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2002 and 2014 nearly 50% did not meet American Society of Clinical Oncology defined criteria for 'clinically meaningful to patients'[9] and the median improvement in OS was less than 10 weeks. Using 'approval' and other 'hard' endpoints as a measure of success detracts from important outcomes such as quality of life and toxicity. Patients with advanced HCC have terminal cancer and improvement in quality of life is a crucial aim of treatment that has not been adequately demonstrated in HCC. The concept of ranking and assessing new drugs based on 'clinical benefit' criteria that takes into account quality of life and toxicity as well as survival benefit is surely the direction in which we should be moving.[10]

The authors also address response rate as a potential surrogate endpoint. The low response rates reported for sorafenib using conventional RECIST criteria appeared to limit the utility of response rate as a signal of drug activity in patients with advanced HCC and prompted the development of modified RECIST (mRECIST), which measures arterially enhanced tumour.[11] However, mRECIST has been variably adopted and of the 21 trials reported in this review, only 5 report mRECIST and only the RESORCE and REFLECT trial report both. Such variable reporting has made cross-trial comparisons challenging. Moreover, mRECIST appears to be more subjective resulting in substantial operator dependence as evidenced by the REFLECT trial in which the partial response rate for lenvatinib according to mRECIST was 23% by investigator and 38% by central review.[12] The limited data directly comparing mRECIST and RECIST 1.1 as a predictor of OS suggests no additional benefit for mRECIST.[13] The advent of immunotherapy for HCC has demonstrated that substantial responses can be achieved using conventional RECIST 1.1 and that these responses translate into impressive survival.[14] Where comparative data are available, the differences between response rates according to RECIST 1.1 and mRECIST are modest; in KEYNOTE-224, overall response rate to pembrolziumab was 17% by RECIST 1.1 and 15% by mRECIST and, in the phase Ib study of atezolizumab and bevacizumab, the overall response rates were 27% and 34%, respectively. Given the current evidence, a compelling case for bespoke response criteria for systemic therapy in HCC has yet to be made. Until mRECIST is demonstrated to be superior to RECIST 1.1 as a surrogate for OS, RECIST 1.1 should be reported to ensure consistency and enable cross-trial comparisons.

Whilst the 'breakthroughs' reported in past 2 years are great news for patients, it is sobering to reflect on the many failures and to remember that, 10 years after the SHARP trial, according to current guidelines,[15] sorafenib remains the standard first-line systemic therapy for advanced HCC. The systematic analyses that have been undertaken here provide important lessons that will inform trial design for the future. Further robust validation of surrogate endpoints will be key to improving the efficiency and reducing the cost of drug development in HCC. In the meantime, several ongoing trials have elected to use so called 'co-primary endpoints' including both OS and PFS or response rate, and these will provide further insights into the relationship between these endpoints.

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Authors' contributions

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Supplementary data

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