plus bevacizumab therapy for hepatocellular carcinoma. However, we believe a meticulous discussion regarding adjuvant therapy for hepatocellular carcinoma is warranted.

First, we are concerned that the gain in recurrence-free survival in the atezolizumab plus bevacizumab group was negated by catch-up recurrence during the off-treatment period beyond 12 months. This finding suggests that recurrence or death was merely delayed, but not reduced, in the atezolizumab plus bevacizumab group. Second, the safety profile of atezolizumab plus bevacizumab might not be tolerable as an adjuvant therapy. In the atezolizumab plus bevacizumab group, there were grade 3–4 adverse events in 136 (41%) of 332 patients and, in 122 (37%) patients, adverse events led to withdrawal from atezolizumab or bevacizumab, or both. Furthermore, two patients died as a result of treatment-related adverse events. Considering the uncertain benefit of this drug combination on overall survival, the risk–benefit balance of adjuvant atezolizumab plus bevacizumab therapy seems questionable.

In our previous randomised controlled trial, adjuvant autologous cytokine-induced killer cell therapy prolonged both recurrence-free survival (hazard ratio 0·63) and overall survival (hazard ratio 0·21).[2] Notably, there were no adverse events leading to treatment discontinuation or treatment-related mortality in the group treated with cytokine-induced killer cell therapy. An extended follow-up study also showed that the gain in recurrence-free survival was sustained for up to 5 years after cessation of repeated cytokine-induced killer cell transfer (ie, 16 times during 14 months).[3] Nonetheless, cytokine-induced killer cell therapy was evaluated solely in South Korean patients, emphasising the imperative need for global trials.

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Following the results of the IMbrave150 study, which reported a significant improvement in overall survival with the regimen of atezolizumab plus bevacizumab versus sorafenib in advanced hepatocellular carcinoma,[1] Shukui Qin and colleagues[2] reported the interim results of the IMbrave050 study, in which the same regimen was administered in the adjuvant setting after tumour resection or ablation in patients with hepatocellular carcinoma at high risk of recurrence. Accordingly, recurrence-free survival (RFS) was improved in those who received atezolizumab plus bevacizumab (RFS median, not evaluable [NE]; [95% CI 22·1–NE]) in comparison with surveillance (median, NE; [21·4–NE]), giving a reduction in disease recurrence of 12·5% (95% CI 5·6–19·5) at 12 months. However, this study raises several questions.

First, the definition of patients with hepatocellular carcinoma at high risk of recurrence included only tumoural features and did not include underlying liver disease features, which are important prognostic determinants. In addition, those criteria differed between patients with resected and ablated tumours. Second, 14.8% of the recruited patients did not meet the Barcelona Clinic Liver Cancer (BCLC) criteria for surgery or ablation.[3] However, at the same time, these are the patients usually considered at higher risk of recurrence. Whether this study had the power to detect differences in RFS in such a small group of patients (BCLC stage B or C) is questionable. Third, the length of the follow-up was short, with the median RFS not yet reached. After 18 months, the RFS curves overlapped, indicating that follow-up should be longer. Fourth, evidence is emerging on the development of resistance in patients treated with atezolizumab plus bevacizumab.[4] Up to 22% of the patients in the IMbrave150 study had disease progression due to complex and still unclear mechanisms of resistance. Clearly, this proportion of patients treated in the adjuvant setting would not be eligible to receive the same regimen in case of recurrence. Lastly, in the adjuvant setting with patients that should be considered cured by surgical resection or ablation, the reported toxicity is a concern; adverse events occurred in 326 (98%) of 332 patients overall, with severe adverse events (grade 3–4) in 136 (41%), resulting in the withdrawal of treatment for 207 (62%) patients overall.

Although the study of Qin and colleagues[2] is encouraging in the context of adjuvant therapy for hepatocellular carcinoma, we believe that clarification of selection criteria and molecular mechanisms is required to aid in the evaluation of the role of immunotherapy in resected patients with hepatocellular carcinoma.

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We have read the Article by Shukui Qin and colleagues,[1] and although we strongly agree with the authors' views and conclusions, we still have some doubts. R0 surgical resection means that margins are grossly and microscopically negative for residual tumour. However, the Article did not mention the effect of the resection margin on postoperative recurrence of hepatocellular carcinoma. Patients with wide resection margins have been shown to have a lower rate of postoperative recurrence and better survival than patients with narrow resection margins.[2] In the current hepatectomy, liver resection is also done with the surgical goal of a wide margin. The width of the resection margin should also be included as one of the factors influencing postoperative recurrence. If the resection margin is not defined, the conclusion might not be definitive.

In this study, tumour recurrence was evaluated on the basis of imaging tests such as CT and MRI. In clinical work, the assessment of treatment outcomes generally requires both imaging tests and analysis of tumour markers (eg, alpha fetoprotein and PIVKA-II). Our centre's study found that alpha fetoprotein might have higher sensitivity to treatment effects.[3] Therefore, we think that relying only on imaging tests to diagnose recurrence after surgery is insufficiently comprehensive, as some patients have increases in tumour markers with negative imaging. In summary, the assessment of postoperative criteria for high risk of recurrence and the criteria for evaluating tumour recurrence in patients with hepatocellular carcinoma require further discussion.

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We read with great interest the Article by Shukui Qin and colleagues[1] on the IMbrave 050 trial, which examined the implications of testing adjuvant immunotherapy with atezolizumab plus bevacizumab for patients at high risk of recurrence of hepatocellular carcinoma following potentially curative therapy. This trial is the first large phase 3 study showing a protective effect of adjuvant immunotherapy treatment for hepatocellular carcinoma. However, there are some considerations that warrant discussion.

First, this study showed that adjuvant treatment with atezolizumab plus bevacizumab conferred a statistically significant and clinically meaningful improvement in recurrence-free survival (RFS), compared with active surveillance, in patients with hepatocellular carcinoma who underwent treatment with a curative intent (resection and ablation). However, the most relevant clinical endpoint in oncology trials, overall survival, could not be reached in the study.[2]

Second, the study showed that some degree of adverse event occurred in 326 (98%) of 332 patients who had received atezolizumab plus bevacizumab; 29 (9%) even discontinued the treatment due to adverse events, and only 23 (7%) showed improvement in RFS. The patients in this study also needed to present themselves for investigations, imaging, immunotherapy infusions, and subsequent treatment relating to the aforementioned adverse events. These requirements affect the health-related quality of life (HRQOL) in patients with hepatocellular carcinoma. HRQOL is a multidomain concept representing the patient's general perception of illness and treatment on various aspects of life and is a recognised clinically relevant endpoint.[3] Therefore, considering RFS without taking overall survival and HRQOL into account makes real-world extrapolation of the study implications unclear.

Third, more than 60% of patients in the study had hepatitis B, and only 11% of patients had non-viral hepatocellular carcinoma. Recent data have shown that metabolic dysfunction-associated steatotic liver disease is now becoming the most common cause of liver disease leading to hepatocellular carcinoma in various parts of the world.[4] Clinical data from several phase 3 trials suggest that immune checkpoint-based therapy is usually more effective in patients with hepatocellular carcinoma with underlying viral disease (ie, infection with hepatitis B virus or hepatitis C virus) than in those with non-viral causes (ie, mainly alcohol, non-alcoholic fatty liver disease, or non-alcoholic steatohepatitis).[5] Thus, the inference of the IMbrave50 study might not apply to all cases of hepatocellular carcinoma. A recently published meta-analysis of 5400 patients showed a significantly higher objective response rate but similar progression-free survival and overall survival among