Liver cirrhosis is the major risk factor for the development of hepatocellular carcinoma (HCC) and with the improving survival of cirrhotic patients a rise in the number of HCC cases is being reported worldwide. Early stage HCC can be treated with curative intent by surgical resection, percutaneous ablation or liver transplantation, but most HCCs are still diagnosed at an advanced stage when curative approaches are not feasible and mortality is consequently high [1]. Over the past few years, novel treatment options based upon a new and improved understanding of the molecular pathogenesis of HCC are being developed. Many of these novel molecular therapies target growth and angiogenic factors, their tyrosine kinase receptors, and their downstream intracellular signal transduction and cell cycle control pathways. Since the positive results from the large Phase III studies of the receptor tyrosine kinase inhibitor, sorafenib [2,3], overall expectations for further improvements in the outcomes of patients with intermediate and advanced stage HCC have been heightened, and the door has been opened for the development and testing of additional small molecule signaling pathway antagonists as targeted therapies for HCC with the goal of achieving similar or better response rates and/or fewer adverse events.

The results of a Phase II open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma [5] with the anticipation of a high response impact and better survival rates for patients. Brivanib is an orally available selective dual inhibitor of the fibroblast growth factor 2 (FGF-2) and vascular endothelial growth factor (VEGF) signaling pathways. Brivanib not only has strong anti-angiogenic effects but also has potent direct effects on tumor cells as shown in subcutaneous mouse HCC xenograft models [5]. FGF is a potent angiogenic factor in HCC and evidence suggests that the upregulation of alternate pro-angiogenic signals such as the FGF pathway, may play a role in tumor resistance to VEGF-targeted anti-angiogenic therapy [6]. Combined inhibition of the VEGF and FGF pathways may therefore be an ideal strategy to prevent or delay resistance to anti-angiogenic therapy. Brivanib may also have efficacy as a second line therapy in HCC patients previously treated with sorafenib [7].

The Phase II study of brivanib involved a mixed population of 55 patients who were two-thirds Asian (64%) and one-third Caucasian (33%). The 6-month progression-free survival (PFS) rate was 18.2%, the median progression-free survival was 2.7 months, and the median overall survival was 10 months. The PFS and 6-month PFS were lower than anticipated at the study onset, when the trial was planned to be deemed as having a positive outcome if the 6-month PFS exceeded 35%. After the study was initiated, the results of the Phase III study of sorafenib in the Asia-Pacific region were reported, showing a significantly lower PFS of 2.8 months compared to the PFS observed in the treated arm of the SHARP study. Considering that 64% of patients in the brivanib Phase II study were Asian, the PFS of 2.7 months observed in this study is likely comparable to the time to progression of 2.8 months observed in the Phase III study of sorafenib in patients from the Asia-Pacific region [3]. The median overall survival in this Phase II study of brivanib of 10 months is a remarkable finding for a population with advanced stage HCC and is encouraging compared to the median overall survival of 9.2 months observed in the Phase II study of sorafenib in patients with advanced HCC and the median survival of 10.7 months observed in the SHARP study [2,8]. The overall survival of 10 months is particularly notable given the high proportion of Asian patients, since the overall survival seen in the Asia-Pacific sorafenib study was 6.5 months [3].

Although study patients tolerated brivanib with a manageable safety profile, eleven patients (21%) had to stop the medication because of treatment-emergent adverse effects. Fatigue, hypertension, and diarrhea were the most common adverse events reported with incidences of 25%, 25%, and 23%, respectively.
The incidence of hand-foot syndrome in this study was 3.6%, which is low compared to the rates reported in the SHARP [2] and in the sorafenib Asian study where researchers found the hand-foot syndrome in 8% and 10.7% respectively, leading to dose reductions in 5% of patients in the SHARP and 11.4% in the sorafenib Asian study [3]. These rates must, however, be considered preliminary given the relatively small number of patients enrolled in the study; more precise rates will have to await the result of ongoing trials of brivanib in HCC.

Based on the results of this Phase II study, the investigators conclude that brivanib shows promising antitumor activity and a manageable safety profile that warrants its evaluation for use as a first line therapy in patients with advanced stage HCC. The early results of this study presumably contributed to the decisions to proceed with Phase III randomized trials of brivanib compared to sorafenib as first line therapy and brivanib as an adjuvant therapy after local palliative therapy in advanced stage HCC. The results of these ongoing studies will help to better define the role of brivanib as a targeted molecular therapy against HCC.

The new era of targeted therapy for cancers has arrived for HCC, but there is still much work to be done to define the specific roles of the available and novel targeted agents and the patient characteristics, disease stage, and combinations of treatments that should be selected for optimal benefit. These further advances will be eagerly anticipated by the multidisciplinary teams that care for these patients, and most of all, by our patients.

Conflict of interest

L. Roberts has received other research support from Bristol-Myers Squibb.

References