Hepatocellular carcinoma (HCC) is the main cause of death in patients with advanced liver disease. High incidence concentrates in East Asia and sub-Saharan Africa. This relates to the fact that most HCC develop on patients with background liver disease, a quite unique feature when compared with other solid tumours. It is estimated that the epidemiological portrait of HCC will significantly change in the future, with more cases related to non-alcoholic fatty liver disease. In HCC, current evidence in terms of mutational landscape identifies TP53, CTNNB1 and TERT promoter mutations as the most frequently mutated genes. At present, none of them are actionable targets nor can be used as predictive biomarkers. More rare mutations, affecting less than 5% of patients, are under evaluation as predictive biomarkers, such as response to a MEK inhibitor (rafametinib) in patients with RAS mutations. In terms of DNA amplification, different studies have shown that around 10% of HCC patients have high-level amplifications of chromosome 11q13, locus of candidate oncogenes such as CCND1, ORAOV1 or FGF19. Experimental evidence suggests that FGF19 inhibition, one of the ligands of the FGF pathway, has anti-tumoral effects in HCC. Unfortunately, none of the trials testing FGFR inhibition with brivanib was able to show a significant improvement in patient survival. Of note, none of the trials selected patients based on predicted FGF pathway activation. By the end of 2013, four drugs (i.e., sunitinib, erlotinib, linifanib and brivanib) have been unable to improve or parallel sorafenib’s results in randomized controlled trials, despite some of them were reported to have some efficacy signals in phase 2. This includes trials testing drugs in first and second line, as well as in the adjuvant setting. Survival benefits provided by targeting oncogenic addiction loops are expected to add survival benefits to the backbone HCC therapy that currently relies on sorafenib. Its wide inhibitory profile, in addition to an anti-angiogenic effect and good safety profile confirms sorafenib as the benchmark for systemic management of HCC. The bottleneck of this approach will be drug toxicity.

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