Hepatocellular carcinoma (HCC) is the seventh most common cancer and fourth leading cause of cancer related death worldwide (1). Two thirds of patients are not eligible to curative treatment such as hepatic transplantation, radiofrequency ablation and liver surgery. In the advanced setting, sorafenib’s hegemony has recently been challenged by others antiangiogenics [multitarget tyrosin kinase inhibitors (TKI): lenvatinib in first-line, cabozantinib and regorafenib in second-line; and one anti-VEGFR2 monoclonal antibody: ramucirumab in second-line in patients with elevated AFP] (2-7). Despite promising primary results, immune checkpoint inhibitors (ICI) failed to improve overall survival (OS) used in monotherapy in phase III trials (8,9). Recently, the combination of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody) has improved OS, progression free survival (PFS), objective response rate (ORR) and quality of life (QoL) compared to sorafenib as first-line treatment of advanced HCC (10).

Tivozanib is an oral inhibitor of VEGFR-1/2/3, with lower inhibiting capacity on c-kit and PDGFRβ. This TKI, already evaluated in first-line of patients treated for metastatic renal cell carcinoma (mRCC), was more efficient than sorafenib in terms of PFS but not OS (median PFS 11.9 vs. 9.1 months; P=0.042; median OS 29.3 vs. 28.8 months; P=0.105) (11). Recently, it was evaluated against sorafenib in third-line and more in mRCC, with similar improved results (PFS 5.6 vs. 3.9 months; P=0.016) (12). Despite these 2 phase III trials, tivozanib has not yet find a clear position among the various alternatives systemic therapies in mRCC (including immunotherapies and combination of antiangiogenics therapies and immunotherapies).

In the British Journal of Cancer, Fountzilas et al. recently reported results of tivozanib in patients with advanced inoperable HCC. The primary objective of this phase Ib/II study was first to determine the maximum tolerated dose (MTD) in the population of HCC patients (who frequently have cirrhosis and/or impaired liver functions), then to determine the activity, with a primary endpoint for the phase II being 24-week PFS. This protocol is clearly clinically relevant in this kind of frail population who is at higher risk to experience side effects of TKI. For example, the results of the phase III study of sunitinib vs. sorafenib were probably negative due to increased toxicity of sunitinib in this population (13). Interestingly, Fountzilas et al. showed that MTD of tivozanib in the HCC population was indeed slightly different from the usual MTD of tivozanib (1 vs. 1.5 mg), which clearly illustrates the need to conduct specific phase I studies in this population.

The primary endpoint was PFS at 24 weeks, with the initial hypothesis to demonstrate a PFS at 24 weeks higher than 50%. In this first step of the phase II part, after the inclusion of 19 patients, the results failed to reach this level of activity. The median PFS was 24 weeks, with a 24-week PFS probability of 58% (90% CI: 33–76), with a 90% CI clearly overlapping 50%. Hence, the phase II part of the trial failed to reach its primary endpoint.

Even though comparison between studies always remains questionable, ORR with tivozanib was slightly higher compared to lenvatinib and sorafenib (21% vs. 18.8% vs. 6.5% respectively according to RECIST). However, median
OS and PFS were not impressive at 9.0 and 5.2 months respectively, as compared with 10.7 and 5.5 months with sorafenib in the SHARP TRIAL, respectively (2). Moreover, OS and PFS with tivozanib were slightly inferior than lenvatinib (13.6 and 7.4 months, respectively), nivolumab (16.4 and 6.8 months, respectively) and atezolizumab-bevacizumab (not reached and 6.8 months, respectively) in recent phase III trials (4,9,10). Moreover, the limited number of patients and the lack of population characteristics description are not sufficient to compare with these pivotal phase III studies. Indeed, authors failed to provide data on major characteristics such as macro-vascular invasion, BCLC stage; ALBI’s grade and Child-Pugh score.

Another important interest of this study is pharmacodynamic and pharmacokinetic studies. Patients with Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD) showed different percentage decrease of serum VEGFR-2 from days 1 to 15 (30.9%, 40.5% and 27.4% respectively), with no clear correlation with response. In a post-hoc analysis only 6 biopsies were available. They showed higher baseline CD8+ cell infiltration by immunochemistry in responders. Despite the limited number of patients, this is consistent with previous studies and suggest that anti-VEGF agents might have immunomodulatory properties, and that response to antiangiogenics might be influenced by the immune microenvironment. However, we should also recognize that as with many studies in HCC, we have too few biopsies available for translational studies. This is clearly a limitation if we want to pursue conclusive research about potential predictive factors for response.

On the basis of all those limitations, it seems fairly unlikely that tivozanib would find its place in HCC’s therapeutic landscape. The recent major modifications in HCC’s arsenal (atezolizumab-bevacizumab combination, lenvatinib, cabozantinib, regorafenib and ramucirumab) highlights the importance of the combination of immunotherapies and TKIs inhibitors. Even if a study combining tivozanib with durvalumab (anti-PDL-1 antibody) is ongoing, phase III evaluating other combinations are already closed to enrollment, including studies with TKIs which already demonstrated activity in phase III trials in HCC. These other combinations are more likely to convince that the combinations using tivozanib.

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### References


