Editorial Commentary

Tivozanib for hepatocellular carcinoma: not likely a new option

Florian Estrade, Fanny Le Du, Laurence Crouzet, Héloïse Bourien, Léa Muzellec, Julien Edeline

Medical Oncology, Centre Eugène Marquis, Rennes, France

Correspondence to: Florian Estrade. Medical Oncology, Centre Eugène Marquis, Rennes, France. Email: f.estrade@rennes.unicancer.fr.

Comment on: Fountzilas C, Gupta M, Lee S, *et al.* A multicentre phase 1b/2 study of tivozanib in patients with advanced inoperable hepatocellular carcinoma. Br J Cancer 2020;122:963-70.

Submitted Apr 17, 2020. Accepted for publication May 06, 2020.
doi: 10.21037/atm-20-3389
View this article at: http://dx.doi.org/10.21037/atm-20-3389

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 two 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.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3389). JE reports personal fees from Bayer, personal fees from Eisai, personal fees from Roche, personal fees from MSD, personal fees from AstraZeneca, grants and personal fees from BMS, grants from Beigene, personal fees from Ipsen, during the conduct of the study; grants and personal fees from BTG, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Fitzmaurice C, Abate D, Abbasi N, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2019;5:1749-68.
2. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
3. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.

4. Kudo M, Finn RS, Qin S, et al. Lenvatinib versussorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
5. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379:54-63.
6. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.
7. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282-96.
8. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab (Pembro) therapy vs best supportive care (BSC) in advanced hepatocellular carcinoma (HCC): KEYNOTE-240. Ann Oncol 2019;30:iv135-6.
9. Yau T, Park JW, Finn RS, et al. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Ann Oncol 2019;30:v874-5.
10. Cheng AL, Qin S, Ikeda M, et al. IMbrave150: Efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol 2019;30:ix186-7.
11. Tivozanib Versus Sorafenib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma: Results From a Phase III Trial | Journal of Clinical Oncology [Internet]. [cité 26 mars 2020]. Available online: https://ascopubs.org/doi/full/10.1200/JCO.2012.47.4940?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&
12. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. Lancet Oncol 2020;21:95-104.
13. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013;31:4067-75.

Cite this article as: Estrade F, Le Du F, Crouzet L, Bourien H, Muzellec L, Edeline J. Tivozanib for hepatocellular carcinoma: not likely a new option. Ann Transl Med 2020;8(21):1337. doi: 10.21037/atm-20-3389

