# Apatinib in an evolving landscape of antiangiogenics and immune checkpoint inhibitors in advanced hepatocellular carcinoma

**Thanh Nga Thi Doan[1], Vi K. Chiu[2], Ju Dong Yang[3], Daneng Li[4], Andrew Hendifar[5], Arsen Osipov[5], Jeremy Lorber[5], Alexandra Gangi[6], Allan Silberman[6], May Cho[7], Jun Gong[5]**

[1]Division of Hematology and Oncology, Department of Internal Medicine, University of California Los Angeles-Olive View Medical Center, Sylmar, CA, USA; [2]Gastrointestinal Oncology, The Angeles Clinic & Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [3]Division of Digestive and Liver Diseases, Department of Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [4]Department of Medical Oncology, City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [5]Division of Hematology and Oncology, Department of Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [6]Division of Surgical Oncology, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [7]Division of Hematology and Oncology, Department of Internal Medicine, University of California Irvine Medical Center, Orange, CA, USA

*Correspondence to:* Jun Gong. Division of Hematology and Oncology, Department of Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Email: jun.gong@cshs.org.

*Comment on:* Qin S, Li Q, Gu S, *et al.* Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2021;6:559-68.

Received: 19 January 2022; Accepted: 11 February 2022; Published: 30 March 2022.

doi: 10.21037/dmr-22-7

**View this article at:** https://dx.doi.org/10.21037/dmr-22-7

Hepatocellular carcinoma (HCC) is a global public health challenge that accounts for about 85–90% of primary liver cancers and ranks as the 5th most common cancer and 4th most common cause of cancer mortality worldwide (1,2). Its tumor hypervascularity underlies the significant role of angiogenesis in its development, proliferation and metastasis. Therefore, targeting angiogenesis has been a longstanding mainstay treatment for patients with advanced HCC. Furthermore, its complex pathogenesis involves interactions with environmental and genetic factors within a tumor microenvironment characterized by chronic inflammation that results in the dysregulation and impairment of immune tumor surveillance (3).

In 2007 sorafenib, a tyrosine kinase inhibitor (TKI) targeting multiple kinases involved in tumor cell proliferation and angiogenesis, became the first approved anti-angiogenic inhibitor for advanced, unresectable HCC by demonstrating an overall survival (OS) benefit over placebo (4). Over the next decade, another multikinase inhibitor, lenvatinib, was approved on the basis of the phase III REFLECT trial by the Food and Drug Administration in the United States (5). Additional TKIs that have been approved include donafenib as an alternative first-line agent by the Chinese National Medical Products Administration (NMPA), and regorafenib (RESORCE trial) and cabozantinib (CELESTIAL trial) following sorafenib treatment in advanced HCC (6-8). It should be noted that many other TKIs have failed to demonstrate superiority when compared head-to-head against sorafenib in phase III studies including sunitinib (NCT00699374), linifanib (NCT01009593), and brivanib (NCT00858871) (9-11). In 2020 atezolizumab and bevacizumab became the first immunotherapy to demonstrate a superior OS over sorafenib in advanced HCC through the IMBrave150 trial (12).

The outcomes of the phase III AHELP trial (NCT02329860) are timely in an increasingly crowded therapeutic space in the advanced HCC treatment landscape. Qin and colleagues conducted the randomized, double-blind, phase III study across 31 centers in China comparing apatinib with placebo for patients with advance HCC who had progressed on or became intolerant to first line systemic therapy (13). Patients in the experimental arm received apatinib 750 mg daily based on a 28 days treatment cycle. Tumor response was assessed by the Response Evaluation Criteria in Solid Tumors version 1.1 every

two cycles and adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The primary endpoint was OS and secondary efficacy endpoints were 6- and 12-month OS, progression-free survival (PFS), 3-, 6-, and 12-month PFS, time to progression, objective responserate rate (ORR), disease control rate, and proportion of patients with stable disease for 6 weeks or more.

At the time of data cutoff, 7 out of the 400 randomized patients did not received the expected study treatment thus were excluded from the final efficacy analysis set which included a total of 261 patients from the apatinib group and 132 patients from the placebo group. Overall, the demographic characteristics between arms were well balanced. Notably, 41% of patients received sorafenib as first line therapy in both arms. Eighty-five percent in the apatinib group and 80% in the control group had hepatitis B virus (HBV) infection, respectively. Results demonstrated apatinib superiority over placebo with an OS of 8.7 months in the apatinib group versus 6.8 months in the placebo group (hazard ratio or HR 0.785, P=0.048). Similarly, the results for PFS, time to progression, the proportion of patients with an objective response, the proportion of patients with disease control, and duration of response all favored apatinib over placebo. Compared to placebo, the apatinib group showed statistically significant increase in hypertension, hand-foot syndrome, and decreased platelet count attributable to the study drug. Most notably, the patients in this study were all from non-Japan Asia where there are higher rates of HBV infections and aggressive (14). Thus, the achievement of these results is encouraging and has led to the approval of apatinib for second-line treatment in advanced HCC by Chinese NMPA in December 2020.

The results of AHELP should be placed in the context of other developments involving monoclonal antibodies targeting angiogenesis and immune checkpoints inhibitors. Among these is the landmark IMbrave150 study conducted by Finn and colleagues that established the combination of atezolizumab and bevacizumab as the new preferred first-line therapy for advanced HCC with superior OS benefit conferred by this combination over first-line sorafenib (12). With longer median follow-up of 15.6 months, the median OS has been shown to be 19.2 months for atezolizumab and bevacizumab versus 13.4 months for sorafenib (HR 0.66; P=0.0009), which represents the longest median OS ever seen in a phase III first-line HCC trial (15,16).

Prior to the IMbrave150 study, results from immune checkpoint inhibitors (ICI) studies were met with mixed responses (17-19). Interestingly, whereas single-agent ICIs results are lackluster, the use of dual ICIs appears promising as demonstrated by the phase III HIMALAYA trial which showed combination of tremelimumab and durvalumab statistically significantly improved OS compared to sorafenib as a first-line treatment for patients with unresectable HCC based on recent top-line results (20).

Recently, the COSMIC-312 trial which assessed the combination of cabozantinib plus atezolizumab showed improved PFS in patients with untreated HCC versus sorafenib monotherapy. However, the study did not meet its primary endpoint for OS although there was a trend toward superiority for the combination therapy (21). In two phase Ib studies, the ORRs of lenvatinib plus nivolumab, lenvatinib plus pembrolizumab were 54.1% and 36.7% respectively (22,23). An ongoing phase III clinical trial of lenvatinib plus pembrolizumab should further clarify its efficacy and safety in first-line setting for unresectable HCC (NCT03713593). It should be noted that despite growing interest in the development of combination ICI and antiangiogenic TKIs, there are no approved combinations incorporating TKIs and ICIs by regulatory authorities worldwide to date.

It is interesting to note that the Kaplan-Meier survival curves of both groups in AHELP study crossed late for which the authors speculated may be due to subsequent, non-standardized anticancer treatments effect on OS (13). When adjusted for post-study anticancer treatments where more patients in the placebo group received post-study treatments than the apatinib group (43% *vs.* 37%) including targeted therapy (23% *vs.* 16%), the HRs for OS were lower compared with those in the primary analysis, reinforcing the superiority of apatinib over placebo. However, in the current era with multiple agents having proven efficacy in the refractory HCC setting, it is clear that placebo as used in the AHELP study is no longer an appropriate control arm in the second-line setting. It should be noted that most patients in the apatinib arm were pretreated with or intolerant to sorafenib, oxaliplatin-based chemotherapy, or both. Oxaliplatin-based chemotherapy is not a commonly used systemic therapy in the Western population. Currently, prior treatment with TKI and immunotherapy would be more reflective of a conventional HCC population. The efficacy of apatinib in immunotherapy resistant patients is unknown as they were not included the AHELP study. More than 50% of the world's HCC cases are from China making

 

it endemic to the region in which there is a dire need for more efficacious therapeutic options (24). This could again represent a potential limitation for applicability of apatinib elsewhere in the world as the main risk factors for cirrhosis in European and US patients are hepatitis C virus, alcohol abuse and increasingly, obesity-related non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (24).

Based on the results of the AHELP study, apatinib is also currently being explored in combination with immunotherapy. In the phase II RESCUE study, camrelizumab combined with apatinib demonstrated an ORRs of 34.3% and 22.5% in patients with advanced HCC in the first-line and second-line setting, respectively (25). Currently, the global randomized phase III clinical trial to study this combination versus sorafenib in first-line setting is ongoing (NCT03764293). Its efficacy in post-immunotherapy treated patients should also be explored, where it could occupy a space as first, second, or later lines of treatment after failure of or intolerance to the first-line atezolizumab plus bevacizumab.

In sum, the phase III AHELP trial was a positive trial demonstrating the superiority of the vascular endothelial growth factor receptor 2 (VEGFR2) TKI apatinib over placebo in advanced HCC patients treated with at least one line of prior systemic therapy. Its advancement in combination with immunotherapy or as an agent following prior treatment with immunotherapy-based regimens would be very logical next steps for its clinical development in HCC.

## Acknowledgments

Funding: None.

## Footnote

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

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-7/coif).The 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. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Abate D, 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. Asafo-Agyei KO, Samant H. Hepatocellular carcinoma. Treasure Island (FL): StatPearls Publishing, 2021.
3. Zhou J, Wang W, Li Q. Potential therapeutic targets in the tumor microenvironment of hepatocellular carcinoma: reversing the protumor effect of tumor-associated macrophages. J Exp Clin Cancer Res 2021;40:73.
4. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
5. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
6. Qin S, Bi F, Gu S, et al. Donafenib versus sorafenib in first-line treatment of unresectable or metastatic hepatocellular carcinoma: a randomized, open-label, parallel-controlled phase II-III trial. J Clin Oncol 2021;39:3002-11.
7. 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.
8. 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.
9. 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.
10. Cainap C, Qin S, Huang WT, et al. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2015;33:172-9.
11. Johnson PJ, Qin S, Park JW, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013;31:3517-24.
12. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-905.
13. Qin S, Li Q, Gu S, et al. Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2021;6:559-68.
14. Yip TC, Lee HW, Chan WK, et al. Asian perspective on NAFLD-associated HCC. J Hepatol 2022;76:726-34.
15. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022;76:862-73.
16. Finn RS, Qin S, Ikeda M, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). J Clin Oncol 2021;39:267.
17. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940-52.
18. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-502.
19. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in keynote-240: a randomized, double-blind, phase III Trial. J Clin Oncol 2020;38:193-202.
20. Imfinzi plus tremelimumab significantly improved overall survival in HIMALAYA Phase III trial in 1st-line unresectable liver cancer. Available online: https://www.astrazeneca.com/media-centre/press-releases/2021/imfinzi-and-tremelimumab-improved-os-in-liver-cancer.html.
21. Sternberg A. Cabozantinib plus atezolizumab extends pfs for frontline HCC in cosmic-312 trial. Cancer network. Available online: https://www.cancernetwork.com/view/cabozantinib-plus-atezolizumab-extends-pfs-for-frontline-hcc-in-cosmic-312-trial.
22. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol 2020;38:2960-70.
23. Kudo M, Ikeda M, Motomura K, et al. A phase Ib study of lenvatinib (LEN) plus nivolumab (NIV) in patients (pts) with unresectable hepatocellular carcinoma (uHCC): Study 117. J Clin Oncol 2020;38:513.
24. Anstee QM, Reeves HL, Kotsiliti E, et al. From NASH to HCC: current concepts and future challenges. Nat Rev Gastroenterol Hepatol 2019;16:411-28.
25. Xu J, Shen J, Gu S, et al. Camrelizumab in Combination with Apatinib in Patients with Advanced Hepatocellular Carcinoma (RESCUE): A Nonrandomized, Open-label, Phase II Trial. Clin Cancer Res 2021;27:1003-11.

doi: 10.21037/dmr-22-7
**Cite this article as:** Doan TNT, Chiu VK, Yang JD, Li D, Hendifar A, Osipov A, Lorber J, Gangi A, Silberman A, Cho M, Gong J. Apatinib in an evolving landscape of antiangiogenics and immune checkpoint inhibitors in advanced hepatocellular carcinoma. Dig Med Res 2022;5:6.