CONFLICT OF INTEREST

None.

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REFERENCES

1. Prado VV.Prado, Hernández-Tejero MM.Hernández-Tejero, Mücke MMM.M.Mücke, Marco FF.Marco, Gu WW.Gu, Amoros AA.Amoros, et al. Rectal colonization by resistant bacteria increases the risk of infection by the colonizing strain in critically ill patients with cirrhosis. *J Hepatol*. 2022;76(5):1079–1089.
2. Schechner VV.Schechner, Kotlovsky TT.Kotlovsky, Kazma MM.Kazma, Mishali HH.Mishali, Schwartz DD.Schwartz, Navon-Venezia SS.Navon-Venezia, et al. Asymptomatic rectal carriage of blaKPC producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected? *Clin Microbiol Infect*. 2013;19(5):451–456.
3. Gómez-Zorrilla SS.Gómez-Zorrilla, Camoez MM.Camoez, Tubau FF.Tubau, Cañizares RR.Cañizares, Periche EE.Periche, Dominguez MAM.A.Dominguez, et al. Prospective observational study of prior rectal colonization status as a predictor for subsequent development of Pseudomonas aeruginosa clinical infections. *Antimicrob Agents Chemother*. 2015;59(9):5213–5219.
4. Giannella MM.Giannella, Bartoletti MM.Bartoletti, Morelli MCM.C.Morelli, Tedeschi SS.Tedeschi, Cristini FF.Cristini, Tumietto FF.Tumietto, et al. Risk factors for infection with carbapenem-resistant Klebsiella pneumoniae after liver transplantation: the importance of pre- and posttransplant colonization. *Am J Transplant*. 2015;15(6):1708–1715.
5. Sundaram VV.Sundaram, Shah PP.Shah, Wong RJR.J.Wong, Karvellas CJC.J.Karvellas, Fortune BEB.E.Fortune, Mahmud NN.Mahmud, et al. Patients With Acute on Chronic Liver Failure Grade 3 Have Greater 14-Day Waitlist Mortality Than Status-1a Patients. *Hepatology*. 2019;70(1):334–345.

Akash Roy
Department of Hepatology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh 226014, India

Madhumita Premkumar
Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Address for correspondence: Akash Roy, Assistant Professor, Department of Hepatology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh 226014, India. Tel: +91 9774056722.
E-mail: royakash12@gmail.com (A. Roy)

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Updated Efficacy and Safety Data from IMbrave150: Atezolizumab Plus Bevacizumab vs. Sorafenib for Unresectable Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and remains a significant cause of cancer-related death globally. The incidence of HCC has been on the rise along with a proportionate rising trend in mortality.[1] However, since the landmark sorafenib in advanced hepatocellular carcinoma (SHARP) trial of the efficacy of sorafenib in advanced HCC, there was little progress made in the armamentarium against advanced HCC for almost a decade. The advent of combination immunotherapy opened up a whole new paradigm in the management of HCC. The preliminary results of the IMbrave150 trial, which used a combination of the anti-programmed death-ligand 1 molecule atezolizumab with anti-vascular endothelial growth factor agent bevacizumab (A+B) marked an epoch in the timeline of HCC management. The results of the trial ultimately catapulted the position of the combination as a first-line therapy in the management of advanced HCC.[2,3] At the time of publishing of the initial results of the IMbrave150 after a median 8.6 months of follow-up, the median overall survival (OS) which was one of the co-primary endpoints was not reached in A+B arm while it was 13.2 months with sorafenib, providing a significant reduction in the hazard for death [HR 0.58 (95% CI 0.42–0.79; $P < 0.001$)]. The current study provided an updated post hoc analysis of the follow-up data from the IMbrave 150 trial.

Overall, in the trial, 501 patients were randomized to receive A+B (n = 336) or sorafenib (n = 165). At the time of analysis, 200 were discontinued in the A+ B arm (death = 179, rest lost to follow-up or withdrawal of consent) while 122 were discontinued in the sorafenib arm (death = 99, rest lost to follow-up or withdrawal of consent). The key results of the updated analysis show a median OS of 19.2 months (95% CI 17.0–23.7) in the

Abbreviations: HCC: Hepatocellular carcinoma; OS: overall survival

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A+B arm and 13.4 months (95% CI 11.4–16.9) in the sorafenib arm ($P < 0.001$). The 12 and 18-month survival rates were 67% and 52% with A+B and 56% and 40% with sorafenib. The second co-primary endpoint of the study was progression-free survival (PFS), which was defined as radiological progression or death. Similar to OS, A+ B showed a significantly better median PFS (6.9 months) than sorafenib (4.3 months). The beneficial results of A+B were consistent across various predefined subgroups, including crucial ones like BCLC stages (B and C), macrovascular invasion, extrahepatic spread, and PD-L1 status. The only subgroup in which the beneficial effect of A+B in OS was not seen was in HCC due to non-viral etiologies. A key area of interest with upcoming data of A+B is the adverse events with the combination. Similar to the initial IMbrave150 results, the most common treatment-related adverse events with A+B were proteinuria, hypertension, raised liver enzymes, and fatigue. Overall treatment-related grade 3/4 adverse events occurred in 43% and 46%, while grade 5 events occurred in 2% and <1% of patients in the A+ B and sorafenib arm. An important concern that has been raised with A+B combinations is the potential increased risk of bleeding. Overall, there were five grade 5 gastrointestinal bleeding events, of which only one was attributed to A+B.

This updated analysis demonstrates the longest median OS reported to date with any first-line therapy in treating unresectable HCC. Recent data from real-world studies have demonstrated similar findings, with an expansion of positive results even in patients with impaired liver function and those having received prior systemic therapy.[4] While these promising results lead to an overall exciting time in the management of advanced HCC, some key areas of concern remain. One such domain is the lack of response in non-viral HCC, especially in the face of NASH becoming the driving force of liver disease and HCC globally. Furthermore, cost-effectiveness determinants and applicability in developing nations also remain a challenge to explore.[5] Hence, given the evidence available at this point of time, the combination therapy can be used as a first-line therapy in patients of advanced unresectable HCC, with preserved liver function (CTP-A), good performance status, and close monitoring for response assessment.

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REFERENCES

1. Sayiner MM.Sayiner, Golabi PP.Golabi, Younossi ZMZ.M.Younossi. Disease burden of hepatocellular carcinoma: a global perspective. *Dig Dis Sci*. 2019;64:910–917.
2. Reig MM.Reig, Forner AA.Forner, Rimola JJ.Rimola, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76:681–693.
3. Finn RSR.S.Finn, Qin SS.Qin, Ikeda MM.Ikeda, et al. IMbrave150 investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894–1905.
4. de Castro TT.de Castro, Jochheim LSL.S.Jochheim, Bathon MM.Bathon, et al. Atezolizumab and bevacizumab in patients with advanced hepatocellular carcinoma with impaired liver function and prior systemic therapy: a real-world experience. *Ther Adv Med Oncol*. 2022;1417588359221080298.
5. Chiang CLC.L.Chiang, Chan SKS.K.Chan, Lee SFS.F.Lee, Choi HCH.C.Choi. First-line atezolizumab plus bevacizumab versus sorafenib in hepatocellular carcinoma: a cost-effectiveness analysis. *Cancers (Basel)*. 2021;13:931.

Akash Roy
Institute of Gastrosciences and Liver Transplantation, Apollo Multispeciality Hospitals, Kolkata: 700054, WB, India

Address for correspondence: Akash Roy, Consultant Hepatologist, Institute of Gastrosciences and Liver Transplantation, Apollo Multispeciality Hospitals, Kolkata: 700054, WB, India. Tel.: +91 9774056722.
E-mail: royakash12@gmail.com (A. Roy)

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