Real World Effectiveness of Atezolizumab and Bevacizumab: What Lessons Can We Learn?

Hepatocellular carcinoma accounts for over 800,000 deaths annually and is expected to reach over 1 million by the year 2025.[1] The era of immunotherapy has created a paradigm shift in the management of advanced-stage HCC, with approvals of atezolizumab plus bevacizumab and durvalumab plus tremelimumab.[2,3] In the IMbrave150 trial, atezolizumab plus bevacizumab demonstrated superior overall survival (OS) and progression-free survival (PFS) compared to sorafenib, leading to the establishment of a new global standard of care in unresectable HCC.(3) An updated analysis defined median OS in both arms as 19.2 and 13.4 months, respectively (HR, 0.66; 95% CI, 0.52–0.85).[4]

While these exceptional results have revolutionized the treatment landscape of HCC, there is a continued need to determine if the efficacy observed in clinical trials is observed when these therapies are implemented in clinical practice. After efficacy is established via clinical trials, understanding treatment effectiveness in practice is critical when weighing different treatment options for patients. Real world effectiveness may differ from efficacy for several reasons including differences in provider experience, patient characteristics, treatment protocols, and outcome ascertainment.[5] Providers may have less expertise in HCC management as well as complications related to cirrhosis or HCC; patients may have increased liver dysfunction or comorbid conditions that would not align with trial inclusion and exclusion criteria; and there will be differences in treatment delivery, suboptimal adherence to treatment schedules, and measurement bias when assessing outcomes such as objective responses or adverse events.

Toward this goal, Kulkarni *et al.* reported the first data for safety and effectiveness of atezolizumab plus bevacizumab in an Indian patient population.[6] In brief, they conducted a retrospective cohort study among 67 patients (majority nonalcoholic fatty liver disease (NAFLD) etiology and nearly three-fourths BCLC stage C). The median OS and PFS of the cohort were only 12 and 8 months, respectively, but this was related to nearly two-thirds of the population having Child Pugh B or C cirrhosis—significantly greater degrees of liver dysfunction than represented in the IMBrave150 Trial. When stratified by Child Pugh class, median OS for Child Pugh A, B, and C were 21, 9, and 4 months, respectively. Objective responses were observed in 38.7% of patients, with similar proportions in Child Pugh A and B patients but progressive disease noted in all patients with Child Pugh C cirrhosis. Similarly, grade 3–4 adverse events (AEs) were noted in 20.9% of patients, including 12.5%, 14.0% and 85.7% of Child Pugh A, B, and C patients, respectively. Of the observed AEs, there were 2 patients who experienced variceal bleeding—one with a history of variceal bleeding with variceal ligation and the other with small varices in the setting of main portal vein invasion. These data are important, not only by providing the first Indian experience with the combination but also insights into how this therapy works in patients with significant liver dysfunction.

The study by Kulkarni *et al.* is also complementary to existing literature from other regions of the world, particularly considering recognized geographic variation in HCC epidemiology including underlying liver disease etiology, availability and provider experience with immune checkpoint inhibitors, and treatment practices for HCC management.[7] The AB-Real Study, a global prospectively maintained database of patients treated with atezolizumab plus bevacizumab from Europe, Asia, and the United States, described clinical outcomes among 296 patients with Child Pugh A and ECOG performance status 0–1 who received first-line therapy.[8] Although over two-thirds had BCLC stage C cirrhosis, the proportion of patients with underlying viral-mediated liver disease (hepatitis B or C) was much higher at 65.9%. Median OS and PFS in this cohort were 15.7 and 6.9 months, respectively—numerically but not significantly lower than those reported in the IMBrave150 Trial. Grade 3–4 treatment-related AEs were reported in 23.6% of patients, with 8.4% having bleeding events. In a separate analysis including patients with Child Pugh A and B cirrhosis (no patients with Child Pugh C cirrhosis), the authors reported patients with Child Pugh A disease had higher OS (16.8 vs. 6.7 months) and PFS (7.6 vs. 3.4 months), although similar objective responses (26% vs. 21%).[9] Notably, GI bleeding rates were not associated with Child Pugh class or ALBI grade. In another multi-site retrospective cohort study from Europe including 147 patients, de Castro and colleagues compared outcomes between patients who met IMBrave150 inclusion/exclusion criteria vs. a comparator group who would have been excluded from the trial.[10] They found that patients who would have been excluded had significantly shorter OS (6.0 vs. 15.0 months), shorter PFS (3.7 vs. 8.7 months), and higher risk of hepatic decompensation

Abbreviation: HCC: Hepatocellular carcinoma; OS: Overall survival; PFS: Progression-free survival; NAFLD: Nonalcoholic fatty liver disease; AEs: Adverse events; ALBI: Albumin-bilirubin

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(ascites 39.7% vs. 9.5% and hepatic encephalopathy 13.7% vs. 1.4%).

Across these studies, there are a few consistent observations to note. First, there is expanded use of atezolizumab plus bevacizumab in patients outside of the clinical trial inclusion and exclusion criteria, ranging from 25 to > 50% across studies. One of the most common drivers of this finding is greater degree of liver dysfunction, which reflects the high proportion of patients with Child Pugh B cirrhosis in clinical practice and lack of alternative efficacious treatment options.[11] Although sorafenib, nivolumab, and namodenoson have demonstrated safety in this patient population, none have completed evaluation in a phase III trial, and each have lower response rates than seen with atezolizumab plus bevacizumab.[12–14] Second, studies have shown worse OS and PFS in patients with Child Pugh B than A patients, despite similar objective responses. This is not surprising since liver dysfunction is one of the strongest prognostic factors for patients with HCC and has been incorporated into staging and treatment allocation systems including the BCLC.[15] Notably, there is an ongoing phase III clinical trial evaluating namodenoson versus placebo in patients with Child Pugh B cirrhosis. However, it should be noted that there is heterogeneity within patients with Child Pugh B cirrhosis, and those with Child Pugh B scores of 7 have better prognosis than those with scores of 9.[16] The ALBI (albumin-bilirubin) score, graded from 1 to 3, was developed to provide additional prognostic discrimination over Child Pugh score alone, and this has been consistently reported as an independent prognostic factor among patients treated with atezolizumab plus bevacizumab in real-world settings.[17] Larger real-world studies of atezolizumab plus bevacizumab may be better able to stratify outcomes among patients with Child Pugh B cirrhosis and help differentiate patients with better outcomes who may derive benefit from therapy from those with very poor prognosis in whom therapy is unlikely to be beneficial. Conversely, patients with Child Pugh C cirrhosis have a very high competing risk of mortality from cirrhosis and significant impairment of quality of life, so these patients are classified as BCLC stage D (terminal stage). These patients are typically recommended to undergo best supportive care, as antitumor therapies are unlikely to change their overall prognosis. The data from Kulkarni *et al.* support this recommendation for best supportive care, as most patients reported at least one adverse event, all experienced progressive disease, and overall survival remained dismal.

Fourth, the combination appears to have preserved safety in clinical practice with acceptable proportions experiencing treatment-related AEs including GI bleeding. These data are important given one of the key concerns with bevacizumab is the bleeding risk given its VEGF activity. This concern informed the requirement for an EGD within 6 months prior to randomization as part of the IMBrave150 protocol and recommendations for this practice to continue when implemented in real-world setting.[18] However, the mechanism for GI bleeding in the setting of bevacizumab is related to vascular disruption and not portal hypertension. Therefore, it is unclear if the risk of variceal bleeding would be higher with Child Pugh B than Child Pugh A cirrhosis. Data from existing real-world studies, including the one by Kulkarni *et al.*, do not suggest an association between liver dysfunction and treatment-related AEs including GI bleeding. However, history of prior variceal bleeding and main portal vein invasion have been shown as risk factors for variceal bleeding, both in IMBrave150 and real-world studies, so these factors may help identify those in whom alternative therapies may be considered. Notably, the optimal management of varices (variceal ligation vs. beta-blockade) to safely facilitate treatment with atezolizumab plus bevacizumab is unknown.

One of the patients from the current study had variceal bleeding despite variceal ligation and beta blockade, highlighting the need for more data in this area.

Finally, the Indian experience provides data evaluating with atezolizumab plus bevacizumab in patients with NAFLD-related HCC. Considering there are no readily available treatment selection biomarkers, we are forced to consider clinical factors, such as liver disease etiology and presence of varices, to guide decision making. These data are important considering that a recent study in mouse models of NASH-HCC found that PD-1 monotherapy resulted in the expansion of CD8+/PD-1+ immune exhausted T-cells, suggesting that patients with non-viral HCC may not be able to mount an efficient immune-reconstitution following checkpoint inhibition.[19] This pre-clinical observation has been supported by post-hoc analyses of clinical trial data, suggesting differential benefit of immunotherapy but not tyrosine kinase inhibitors in patients with non-viral etiologies, although a recent post-hoc analysis of IMBrave150 Trial data failed to show any differential effect between metabolic-associated fatty liver disease patients and those with other etiologies.[20,21] Similarly, most real-world data including the Indian experience does not suggest worse responses or survival among patients with non-viral liver disease. It is possible that single agent PD-1 inhibition may experience this limitation, but this can be overridden with combination therapy—whether by VEGF inhibition or addition of CTLA-4 inhibition. Overall, further real-world data and potential stratification of future clinical trials by liver disease etiology is warranted.

In summary, accumulating real-world data, including the Indian experience, demonstrate clinical effectiveness and safety of atezolizumab plus bevacizumab in clinical practice in most patients. We hope that continued generation of global real-world data, both for atezolizumab plus bevacizumab as well as durvalumab plus tremelimumab,

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may identify reliable predictors of who is most likely to benefit and those at highest risk of potential treatment related AEs, allowing us to make decisions more precisely between options in the first-line setting.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

All authors were involved with drafting of the manuscript, critical revision of the manuscript for intellectual content, and study supervision.

CONFLICTS OF INTEREST

Amit Singal has served as a consultant or on advisory boards for Genentech, AztraZeneca, Eisai, Exelixis, Bayer, Boston Scientific, FujiFilm Medical Sciences, Exact Sciences, Roche, Glycotest, Universal Diagnostics, Freenome, and GRAIL.

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