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Safety and Efficacy of Atezolizumab-Bevacizumab in Real World: The First Indian Experience

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Background: **Atezolizumab-bevacizumab (atezo/bev) combination is a recommended first-line systemic therapy for unresectable hepatocellular carcinoma (uHCC). There are no studies from India reporting the safety and efficacy of this drug in real-world settings where most patients present in an advanced stage.** ***Methods:*** **In this retrospective study from two centers in India, we included patients with uHCC who received atezo/bev as first-line systemic therapy. Comparison of overall survival (OS) among the different Child–Turcotte–Pugh (CTP) classes was the primary objective, while progression-free survival (PFS), radiologic response, and adverse events to the therapy were secondary objectives.** ***Results:*** **The median age of the 67 patients who received atezo/bev therapy was 61 (29–82) years, and 86% were males. Nonalcoholic steatohepatitis (55.2%) was the commonest cause of cirrhosis, and most patients belonged to BCLC-C (74.6%%). There were 24 patients in CTP A, 36 in CTP B, and 7 in CTP C. The median OS was 12 (95%CI, 8.16–15.83) months in the cohort. The median OS in CTP class A, B, and C was 21 (95%CI, 0–42.06) months, 9 (95%CI, 5.46–12.53) months, and 4 (95%CI, 2.14–5.85) months, respectively ($P < 0.001$). The median PFS in the whole cohort was 8 (95%CI, 6.03–9.96) months. The median PFS in Child A, B, and C was 18 (95%CI, 0.16–35.84) months, 8 (95%CI, 6.14–9.85) months, and 2 (95%CI, 1.77–2.23) months ($P < 0.001$). On mRECIST evaluation, 12.9% had achieved a complete response, 25.8% had a partial response, 27.41% had stable disease, and the rest had progressed. The objective response rate was 38.7%, and the disease control rate was 66.12%. Of the 64% who developed adverse events, 13.43% discontinued the drug. The incidence of grade ≥3 events was significantly higher in CTP C (85.7%) compared to CTP A (12.5%) and CTP B (14%) ($P < 0.001$).** ***Conclusions:*** **Atezolizumab-bevacizumab is safe and effective in uHCC in real-world settings. Candidate selection is of utmost importance in treating uHCC with atezolizumab-bevacizumab to achieve a good response. Current evidence strongly suggests limited use of atezolizumab-bevacizumab in patients with CTP C, and such individuals should not be considered for this combination therapy. (J Clin Exp Hepatol xxxx;xxx:xxx)**

The incidence of hepatocellular carcinoma (HCC) has significantly increased in recent years in India.[1,2] HCC is one the major contributors to morbidity and mortality for patients with cirrhosis.[2] Tyrosine kinase inhibitors, including sorafenib and lenvatinib, remained the treatment of choice for a long for patients with unresectable HCC (uHCC).[3,4] The median survival with these drugs ranged between 10 and 13.5 months.[3–5] Recent studies have also reported improved progression-free survival (PFS) with lenvatinib (5.2 months) than sorafenib (3.3 months).[6] However, neither of these drugs were effective in achieving a complete response (CR).[4,5] The IMbrave trial was a breakthrough in the management of uHCC.[7] The drugs used in the study were atezolizumab-bevacizumab (atezo/bev), which target programmed death ligand-1 (PD-L1) and vascular endothelial growth factor (VEGF), which inhibit tumor growth through prevention of T-cell suppression and inhibiting angiogenesis and altering tumor microenvironment. The dual blockade of PD-L1 and VEGF leads to enhanced antitumor activity, and the combination of atezo/bev was demonstrated to have more prolonged PFS (5.6 [95% CI, 3.6–7.4] months in the combination group vs. 3.4 [1.9–5.2] months in atezo alone) than single agent atezo in the phase 1 trial.[8] In the phase 3 trial (conducted across the world excluding India), this combination was associated with significant survival benefits (67.2% vs. 54.6%) compared to the sorafenib group.

Keywords: HCC, overall survival, progression-free survival
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Abbreviations: Atezo/bev: Atezolizumab-Bevacizumab; BCLC: Barcelona Clinic Liver Cancer; CTP: Child-Turcotte-Pugh; DCR: disease control rate; ECOG: Eastern Cooperative Oncology Group performance; mRECIST: modified Response Evaluation Criteria in Solid Tumors; ORR: objective response rate; PFS: progression-free survival; uHCC: unresectable hepatocellular carcinoma
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The median PFS was also better with atezo/bev (6.8 months) than with sorafenib (4.3 months) and was reported to be safe. Atezo/bev has now become the first-line approved drug for patients with uHCC who have preserved liver function tests.[9,10] There have been several real-world data on the use of atezo/bev in patients with uHCC from various countries.[11–13] However, there are no studies assessing the safety and efficacy of atezo/bev from India in uHCC. Therefore, we aimed to evaluate the safety and efficacy of atezo/bev in the Indian population.

METHODS

We included the data collected retrospectively from AIG Hospitals, Hyderabad, and Mahatma Gandhi Medical College, Jaipur, from November 1, 2020, to July 1, 2022. The study was approved by the institutional ethics committee vide letter number AIG/IEC-Post BH&R 33/08.2022–01. The primary objective was to assess the overall survival (OS) among the different Child–Turcotte–Pugh (CTP) classes. The secondary objective was to determine the PFS, radiological response, and adverse events due to therapy.

The dosing of atezo/bev in our cohort was as per the IMbrave trial, that is, atezolizumab 1200 mg and bevacizumab 15 mg/kg intravenously every 3 weeks.[7] Treatment was discontinued if the disease progressed or the patients developed drug-related toxicity, died, or underwent liver transplantation. Adverse events were managed as per the hospital protocol and as described by the summary of product characteristics. OS is the duration of survival from the administration of the first dose to death. PFS is the time required for the radiological progression of the disease from the initiation of immunotherapy or death.

Data recorded were baseline demographics, including age, sex, etiology of liver disease, severity scores, including ALBI score, comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, baseline biochemical variables, and imaging characteristics. We included patients who had received prior locoregional therapy.

Radiological assessment was done by triphasic contrast-enhanced magnetic resonance imaging or computed tomography after 3–4 cycles of immunotherapy. All patients also underwent a positron emission tomography-CT (PET CT) scan to evaluate extrahepatic spread prior to initiation of immunotherapy. The radiological response was assessed using modified Response Evaluation Criteria in Solid Tumors (mRECIST).[14] Accordingly, complete disappearance of intratumoral enhancement in all target lesions was considered a CR and at least a 30% decrease in the sum of diameters of viable target lesions compared to the baseline sum of the diameters of target lesions was considered partial response (PR). A ≥20% increase in the diameter of viable target lesions, compared to the baseline smallest sum of the diameters of viable target lesions recorded since

Table 1 Baseline Characteristics of the Included Patients.

Variables	N = 67
Age (years)	61 (29–82)
Males (n, %)	58 (86.5%)
Comorbidities (n,%)	
Diabetes mellitus	24 (35.8%)
Hypertension	25 (37.3%)
Hypothyroidism	6 (9%)
History of variceal bleed (n,%)	1 (1.5%)
High risk varices at baseline (n,%)	6 (9%)
History variceal ligation (n,%)	18 (27%)
Median dose of bevacizumab (mg)	800 (500–1200)
Median number of cycles	3 (1–15)
Etiology of liver disease (n, %)	
NASH	37 (55.2%)
HBV	13 (19.4%)
HCV	11 (16.4%)
Alcohol	5 (7.5%)
Cryptogenic	1 (1.5%)
Baseline α-fetoprotein (ng/ml)	727.3 (2.2–6,00,000)
AFP >400 (ng/ml)	37 (55.2%)
ECOG status (n,%)	
0	40 (59.7%)
1	27 (40.3%)
ALBI score	−2 (−3.2 to −0.74)
ALBI grade (n,%)	
1	31 (46.3%)
2	24 (35.8%)
3	12 (17.9%)
Child-Turcotte-Pugh score	7 (5–13)
Child-Pugh class (n, %)	
A	24 (35.8%)
B	36 (53.7%)
C	7 (10.4%)
BCLC stage (n, %)	
B	6 (9%)
C	50 (74.6%)
D	11 (16.4%)
Extrahepatic spread (n,%)	12 (18%)
Macrovascular invasion	14 (21%)
Both extrahepatic spread and macrovascular invasion	15 (22.4%)
Prior therapies (n, %)	
Transarterial radioembolization (TARE)	4 (6%)
Transarterial chemoembolization (TACE)	3 (4.5%)

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Table 1 (*Continued*)

Variables	N = 67
Microwave ablation (MWA) for adrenal metastasis	1 (1.5%)
Post liver Transplantation recurrence	1 (1.5%)
Post therapy treatment	
Resections	1 (1.5%)

NASH, nonalcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona clinic liver cancer. All continuous variables are expressed as median (range). ALBI, albumin-bilirubin; AFP, alfa-feto protein.

the treatment started, was considered a progressive disease (PD). Lastly, patients who did not qualify for PR or PD would be considered stable disease (SD). Objective response rate (ORR) included CR and PR, while disease control rate included (DCR) SD apart from CR and PR.

Statistical Analysis

The data were analyzed using SPSS ver. 29 (IBM Corp., New York, USA). Continuous data are presented as mean (standard deviation) or median (range) as applicable. Categorical data are expressed as n (%). Kaplan–Meier analysis was carried out to assess the OS and PFS. The comparison between the three groups is done using Log-rank (Mantel-Cox) test and depicted as survival curves.

RESULTS

A total of 107 uHCC patients were screened for atezo/bev combination. Eleven patients with poor ECOG (PS-2) status were denied therapy by the treating physician. Twenty-one patients declined therapy due to lack of finances. Eight patients with a history of systemic therapy with lenvatinib (n = 7) and sorafenib (n = 1) were also excluded. A total of 67 patients (59 from AIG Hospitals, Hyderabad, and eight from Mahatma Gandhi Medical College, Jaipur) were included in the study. The median age of the cohort was 61 (29–82) years. Eighty-six percent of them were males. The most common etiology of cirrhosis was nonalcoholic steatohepatitis (NASH, 55.2%), followed by hepatitis B and C in 19.4% and 16.4%, respectively (Table 1). There were 24 patients in CTP A, 36 in CTP B, and 7 in CTP C. Diagnostic gastroscopy was performed in all patients, of which 17 had large (red color signs in 6) esophageal varices, 36 had small varices (red color signs 7), and 14 had only prominent veins. Eighteen patients had a history of variceal ligation, and beta-blockers were administered in 31 patients (including seven patients with a history of variceal ligation). Each patient received a median of 3 cycles[1–15] of atezo/bev during the study period. Four patients had undergone Y90-transarterial radioembolization (TARE), three had undergone transarterial chemoembolization (TACE), and one had undergone microwave ablation for adrenal metastasis. One of the patients had received liver transplantation 7 months prior for alcohol-related liver disease and HCC (within Milan's; Pre-LT AFP- 213 ng/ml).

Primary Objective

The median OS was 12 (95%CI, 8.16–15.83) months in the whole cohort. The median OS in CTP class A, B, and C was 21 (95%CI, 0–42.06) months, 9 (95%CI, 5.46–12.53) months, and 4 (95%CI, 2.14–5.85) months, respectively ($P < 0.001$) (Figure 1a). The median OS in ALBI grade 1 was 21 (95%CI, 4.58–37.41) months, while it was 9 (95%CI, 4.11–13.88) months in grade 2 and 4.19 (95%CI, 0–15.22) months in ALBI grade 3 ($P = 0.005$) (Figure 1b). Over a median follow-up of 12 (95%CI, 8.16 to 15.83) months, 40.3% had died. Mortality in CTP A was 20.8% compared to 44.4% in CTP B and 85.7% in CTP C ($P = 0.007$).

PFS

The median PFS in the cohort was 8 (95%CI, 6.03–9.96) months. The median PFS in Child A, B, and C was 18 (95%CI, 0.16–35.84) months, 8 (95%CI, 6.14–9.85) months, and 2 (95%CI, 1.77–2.23) months ($P < 0.001$) (Figure 2a). The median PFS in ALBI class 1, 2, and 3 were 18 (95% CI, 2.64–33.35) months, 9 (95%CI, 2.54–15.45) months, and 7 (95%CI, 0–20.7) months, respectively ($P = 0.08$) (Figure 2b).

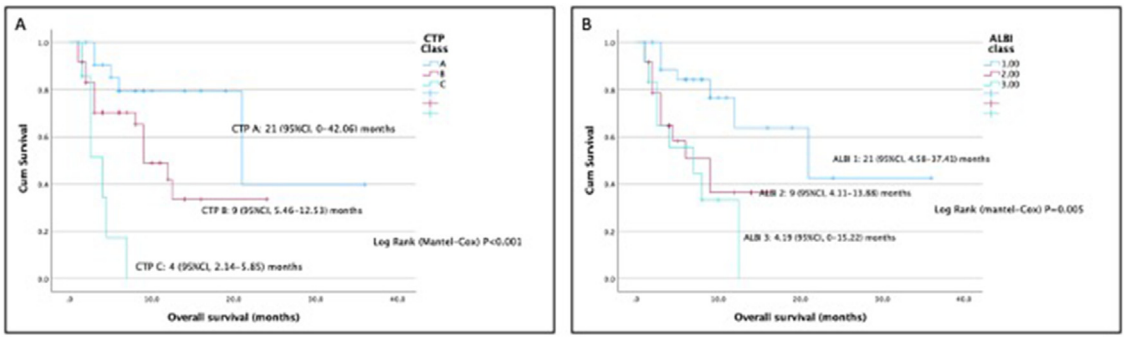

Figure 1 Kaplan-Meier curve depicting the overall survival among different Child–Turcotte–Pugh (CTP) classes (A) and ALBI classes (B).

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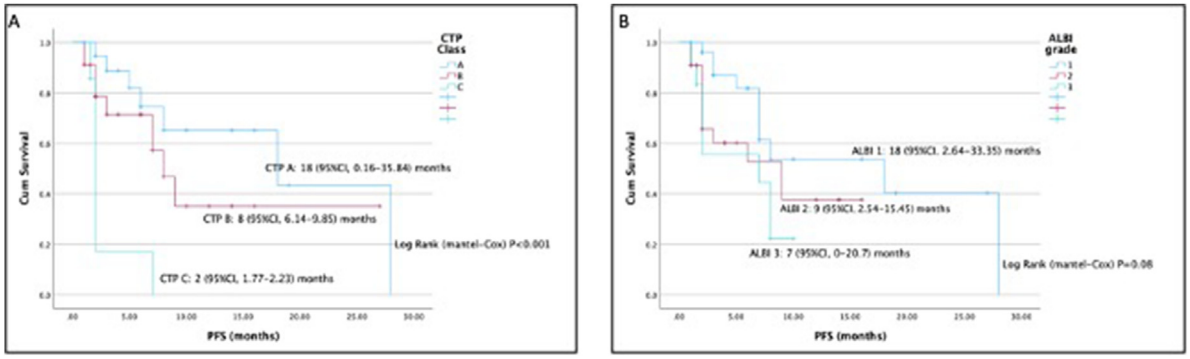

Figure 2 Kaplan-Meier curve depicting the progression-free survival (PFS) among different Child classes (A) and ALBI classes (B).

Radiological Response

A total of 62 patients underwent radiological evaluation. On mRECIST evaluation, 8 (12.9%) had achieved CR, 16 (25.8%) had PR, 17 (27.41%) had SD, and the rest, 21 (33.87%), had PD. In total, ORR was 38.7% (24/62), and DCR was 66.12% (41/62). Of the 21 who had progressed, three were started on lenvatinib, who did not tolerate the drug, and the drug was withdrawn. All patients in CTP C progressed, while the response among CTP A was slightly higher than CTP B (Table 2).

Of the four patients who had undergone TARE prior to atezo/bev therapy, two achieved CR, and two achieved PR. Of the three patients who had undergone prior TACE, two patients progressed despite systemic therapy, while one remained stable. The post-transplant patient has received six doses and is currently having SD without any alterations in liver chemistries. He is being managed with tacrolimus (2 mg/day), mycophenolate mofetil (1000 mg/day), and everolimus 1 mg/day.

Adverse Events

A total of 43 (64.2%) patients developed adverse events due to drug therapy. Most common adverse event was fatigue, noted in 11 patients and seven patients developed a progressive rise in serum bilirubin levels (Table 3). A total of 14 (21%) patients developed grade 3 adverse events. The drug was discontinued in 10 patients due to adverse events (rise in bilirubin levels - 7, fatigue - 1, and variceal bleed - 2). Of the two patients who had a variceal bleed, one of them had a history of variceal bleeding prior to therapy and had undergone two sessions of variceal ligation prior to therapy and was on beta-blocker therapy, while the second patient had small varices prior to therapy and had main portal vein tumoral thrombosis. Both patients belonged to CTP A. The incidence of (any grade) adverse events in CTP A was 62.5% (15/24), 61.1% (22/36) in CTP B, and 85.7% (6/7) in CTP C (P = 0.45). However, the incidence

Table 2 Best Radiological Response to the Therapy.

Response to therapy	Overall (n,%) out of 62 patients	CTP A (of 24)	CTP B (of 32)	CTP C (of 6)
CR	8 (12.9%)	4 (16.7%)	4 (12.5%)	0
PR	16 (25.8%)	7 (29.2%)	9 (28.12%)	0
SD	17 (27.41%)	8 (33.3%)	9 (28.12%)	0
PD	21 (33.87%)	5 (20.8%)	10 (31.25%)	6 (100%)
ORR	24 (38.7%)	11 (45.83%)	13 (40.62%)	–
DCR	44 (66.12%)	19 (79.16%)	22 (69.75%)	–

CR, complete response; CTP, Child-Turcotte-Pugh; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate. (4 in CTP B and 1 in CTP C could not be evaluated).

Table 3 Adverse Event due to Atezolizumab/Bevacizumab.

Adverse event	Any grade	≥3 grade
Total	43 (64.2%)	14
Fatigue	12	1
Rise in bilirubin >3 mg/dl	7	7
Hypertension	5	2
Fever	5	0
Ascites	4	2
Arthralgia	3	0
Loss of appetite	3	0
Oral ulcers	3	0
Skin rash	3	0
Myalgia	2	0
Nausea	2	0
Variceal bleed	2	2
Pruritus	1	0
Diarrhea	1	0
Hypothyroidism	1	0
Rise in AST/ALT	1	0
Epistaxis	1	0

ALT, alanine transaminase; AST, aspartate transaminase.

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Table 4 Incidence of Grade ≥3 Events According to CTP Class.

Grade ≥3 events	CTP A (n = 24)	CTP B (n = 36)	CTP C (n = 7)
Fatigue	0	0	1
Rise in bilirubin >3 mg/dl	1	2	4
Hypertension	0	1	1
Variceal bleed	2	0	0
Ascites	0	2	0
Total	3 (12.5%)	5 (14%)	6 (85.7%)

CTP, Child-Turcotte-Pugh.

of grade ≥3 events was significantly higher in CTP C (85.7%) compared to CTP A (12.5%) and CTP B (14%) ($P < 0.001$) (Table 4).

DISCUSSION

The salient features of this study are (a) atezo/bev combination therapy is an excellent option for patients with uHCC with ORR of 38.7% and DCR of 66.12%; (b) survival and response to therapy are dependent on the severity of liver disease; (c) CTP C patients are not candidates for atezo/bev combination.

In the IMbrave trial, only CTP A patients were included and did not achieve OS when the trial was first reported. Most patients in the real-world present at an advanced stage, limiting the therapeutic options. There are several studies reporting the safety and efficacy of the atezo/bev combination in CTP B.[11,13,15–17] Few studies have also reported the real-world efficacy of the drug in CTP C patients.[15,18,19] The median OS (12 months) and PFS (8 months) noted in our study are similar to the previously reported studies, which included all classes of CTP.[15,18] The incidence of adverse events was slightly higher in CTP C although it did not reach statistical significance due to the smaller sample size. The survival of a patient is dependent on CTP class, that is, liver function.[19,20] Therefore, compassionate use of atezo/bev or any other systemic therapy should be curtailed in patients with CTP C. ALBI score is an excellent objective score to assess the liver function in patients with HCC and predicts the outcome of these patients.[21] Similar to the previous studies, the ALBI score predicted OS and PFS in our cohort.[13,22]

The risk of variceal bleeding is the most feared complication of bevacizumab therapy. We performed screening endoscopies on all patients. Only two patients had variceal bleeding and discontinued the treatment. The risk of variceal bleeding reported in the literature varies from 1 to 10%.[7,19,23] In the study by D'Alessio *et al.*, screening endoscopy was performed in only 50% of patients. Furthermore, the authors reported that the presence or absence of varices pretreatment did not predict bleeding, which we partially agree with as the risk of bleeding in our cohort was also lower. However, we suggest that patients with a history of variceal bleeding and those with portal vein thrombosis should be cautiously monitored for variceal bleeding.

The combination of locoregional therapy with the atezo/bev combination is an upcoming strategy to achieve a CR and prolong survival.[24] In our study, patients who received Y90-TARE followed by atezo/bev therapy, achieved 100% ORR. A large multicenter trial to assess the efficacy of Y90 TARE with atezo/bev combination is underway (ClinicalTrials.gov Identifier: NCT04541173). The rationale behind this is the heterogenous tumor microenvironment which leads to inconsistent outcomes noted with immune-checkpoint inhibitors alone. Y90-TARE leads to enhanced antigen presentation, which will then be targeted by atezolizumab, and tumor suppression would be further augmented by bevacizumab which prevents angiogenesis and reduces immunosuppressive immune infiltrate.

LIMITATIONS AND FUTURE DIRECTIONS

The study included only 67 patients retrospectively from a single center, which is less compared to the burden of the disease in our country. It may be argued that CTP C is a contraindication for systemic therapy, given the high risk of adverse events, and should not have been administered in the first place. However, the aim of the retrospective study was to highlight that candidate selection is of utmost importance in treating uHCC with systemic therapy to achieve a good response. We did not compare the efficacy of atezo/bev with other first-line therapy nor we included those receiving atezo/bev as second-line systemic therapy, which merits further multicenter studies. Furthermore, reports of higher graft rejection in patients with uHCC receiving immunotherapy post-transplant are reported, which was not noted in our study.[25,26] However, none of these patients in previous studies had received atezo/bev for HCC recurrence post-transplant.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

AVK and KK prepared the initial draft; Data collection by AS, PC, VK, MS, BP, AK, and AVK; Radiological assessment by AP; AVK, MS, PNR, and DNR critically assessed the manuscript and edited. All members approved the final draft.

CONFLICTS OF INTEREST

All authors have none to declare.

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