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ORIGINAL RESEARCH

Atezolizumab Plus Bevacizumab in Patients with Unresectable Hepatocellular Carcinoma: Real-World Experience From a US Community Oncology Network

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Purpose: Atezolizumab plus bevacizumab (atezo-bev) is a preferred first-line (1L) systemic therapy option for unresectable hepatocellular carcinoma (uHCC). However, evidence of its effectiveness in real-world clinical practice, including in patients with impaired liver function, remains limited.

Patients and Methods: This retrospective observational study included adult patients who initiated 1L atezo-bev for uHCC within The US Oncology Network between 1/1/2019 and 8/31/2022 using structured and unstructured electronic health records data. Overall survival (OS) and real-world progression-free survival (rwPFS) were assessed using Kaplan-Meier methods for the overall cohort and in a subgroup of "trial-like" patients with characteristics that were consistent with those of the IMbrave150 Trial (ECOG performance status 0–1, Child-Pugh class A, albumin-bilirubin grade 1–2).

Results: Overall, 374 patients met eligibility criteria (mean age 68.8 years, 78.9% male, 31% Child-Pugh class B-C among reported, 18% ECOG performance status ≥2 among reported), of whom 132 patients comprised the trial-like subgroup. At a median follow-up of 5.6 months, median (95% CI) OS was 13.2 (9.5, 15.9) months and rwPFS was 6.4 (5.1, 7.7) months. In the trial-like subgroup, median (95% CI) OS was 16.5 (13.2, NR) months and rwPFS was 9.4 (5.7, 12.5) months.

Conclusion: Atezo-bev was used as 1L systemic therapy for HCC in a diverse patient population across US community oncology settings. Real-world effectiveness of atezo-bev among trial-like patients is comparable to that reported in the Phase 3 study. These data can help guide selection of appropriate treatment candidates and maximize the benefits of atezo-bev in routine clinical practice.

Keywords: advanced HCC, first-line, systemic treatment, real-world evidence

Introduction

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver which most commonly occurs in patients with chronic liver disease and cirrhosis.[1] Risk factors for HCC include viral hepatitis including hepatitis B virus (HBV) and/or hepatitis C virus (HCV), chronic alcohol consumption, and other conditions such as metabolic dysfunction associated steatotic liver disease (MASLD).[1] Patients with HCC generally have a poor prognosis, with overall 5-year survival rates reported to be approximately 20%.[2]

Upon diagnosis, patients should be evaluated in multidisciplinary settings for potentially curative approaches such as surgical resection, liver transplant or local ablative therapy, although many patients with HCC have advanced disease requiring systemic therapy. Preferred first-line (1L) treatments shifted from tyrosine kinase inhibitors to immunotherapy-based regimens after the introduction of atezolizumab plus bevacizumab (atezo-bev), approved by the US Food and Drug

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Administration (FDA) in May 2020, followed by tremelimumab plus durvalumab which was approved in October 2022.[3] FDA approval of atezo-bev was granted based on results from the Phase 3 IMbrave150 Trial.[3,4] Median (95% confidence interval [CI]) progression-free survival (PFS) was 6.8 (5.7–8.3) months in the atezo-bev arm and 4.3 (4.0–5.6) months in the sorafenib arm (hazard ratio [HR]: 0.59; 95% CI: 0.47–0.76; P<0.001).[4] Updated IMbrave150 results demonstrated that the median (95% CI) overall survival (OS) was 19.2 (17.0–23.7) months in the atezo-bev arm and 13.4 (11.4–16.9) months in the sorafenib arm (HR: 0.66; 95% CI: 0.52–0.85; P=0.0009) with landmark OS at 18 months of 52% in the atezo-bev arm and 40% in the sorafenib arm.[5]

Despite the superior efficacy of atezo-bev relative to the previous standard of care demonstrated by the IMbrave150 Trial, there is a continued need to understand the real-world use and effectiveness of atezo-bev in clinical practice. Real-world data is particularly important as clinical practice may vary from clinical trial protocols in terms of the timing and frequency of monitoring, adherence to treatment, and management of complications. Real-world effectiveness may differ from clinical trial efficacy due to differences in patient characteristics. For example, patients with Child Pugh (C-P) class B-C or Eastern Cooperative Oncology Group Performance Status (ECOG PS) >2 are typically excluded from clinical trials. Moreover, trials for HCC have historically lacked racial, ethnic, and socioeconomic diversity, limiting our understanding of treatment responses across different minority groups. While there is some emerging evidence of real-world effectiveness outside the US and in academic institutions, there are limited data in the US community oncology setting on the use and effectiveness of atezo-bev for first-line (1L) systemic treatment of patients with unresectable HCC (uHCC), including those with impaired liver function. Therefore, this study aims to describe demographic and clinical characteristics, treatment patterns, and clinical outcomes of patients diagnosed with uHCC and treated with 1L atezo-bev in real-world practices.

Materials and Methods

Study Design and Data Sources

This was a retrospective observational study of adult patients with HCC treated with 1L atezo-bev within The US Oncology Network, a large community oncology network comprised of over 2400 providers in more than 500 sites of care across the US.[6] Data were sourced from structured fields of The US Oncology Network's iKnowMed (iKM) electronic health record (EHR) and were supplemented with unstructured data abstracted from patient charts for measures such as the physician-documented C-P class, treatment history, and physician-assessed response. The Limited Access Death Master File (LADMF) was also accessed for additional information on vital status and death. Eligibility criteria included patients at least 18 years of age at first diagnosis of HCC, at least 2 visits within the US Oncology Network during the study observation period (June 1, 2020 - November 30, 2022), and initiation of 1L atezo-bev for HCC (index event) during the study identification period (June 1, 2020 - August 31, 2022). Initiation of atezolizumab and bevacizumab were required on the same day or within 42 days of each other. Patients were excluded from the study if they were enrolled in clinical trials, treated for other documented primary cancers during the study observation period, received a liver transplant any time prior to or during the study observation period, or underwent surgery within 6 months prior to the index date.

Patient Characteristics and Outcomes

Demographic and clinical characteristics included age, sex, race and ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic, Asian), ECOG PS, alpha-fetoprotein (AFP), albumin-bilirubin (ALBI) grade (1, 2, 3), C-P class (A, B, C), and liver disease etiology (viral, non-viral). C-P class was reported as documented in the charts. For patients with no physician-documented C-P class, we derived C-P score based on laboratory results and risk factors assessed within 90 days prior to index or the earliest value after the index date (ie, date of atezo-bev initiation).[7,8] Treatment regimens during the study observation period were assessed up to third-line (3L). Additional treatment patterns included type and frequency of locoregional therapy (LRT), type and timing of bevacizumab initiation, treatment disposition and reason for discontinuation of 1L atezo-bev. Clinical effectiveness was assessed using progression-free survival (rwPFS) and OS. rwPFS was measured from index to the earliest date of physician-documented progression or death due to any cause. OS was defined as the interval between the index date and date of death due to any cause as documented in the EHR or LADMF.

Statistical Analysis

Descriptive analyses were performed on patient characteristics and treatment patterns. Kaplan-Meier methods were used to assess clinical effectiveness outcomes for the overall cohort and in a "trial-like" cohort of patients with certain clinical characteristics that were consistent with the IMbrave150 Trial (C-P class A, ALBI grade 1–2, and ECOG PS 0–1). Additional exploratory subgroups analyses were conducted by C-P class, ALBI grade, etiology, and race/ethnicity. Patients who did not experience an event were censored on the last contact date during the study observation period. Analyses were conducted using SAS v.9.4 (SAS Institute, Inc; Cary, NC, USA).

Results

Patient Characteristics

Within The US Oncology Network, there were 514 adult patients identified with a documented diagnosis of "hepatocellular carcinoma" or "liver cancer" who initiated 1L atezo-bev for HCC during the study identification period. Among them, 402 patients met additional eligibility criteria using structured EHR data and were selected for chart abstraction. Upon verification of eligibility criteria, 374 patients were included in the study, of whom 132 comprised the "trial-like" subgroup.

Patient characteristics are reported in Table 1. The mean (standard deviation [SD]) age at index was 68.8 (8.9) years, 69.3% were age ≥65 years, 78.9% were male, and 48.4% were non-Hispanic White. ECOG PS was documented at baseline (within 30 days of index) in 291 patients, of whom 239 (82.1%) had an ECOG PS of 0–1 and 52 (17.9%) had ECOG PS ≥2. There were 192 (51.3%) patients with viral disease etiology, and 70 (18.7%) patients with non-viral liver disease. Of the 192 patients with viral liver disease, 172 (89.6%) had HCV and 28 (14.6%) had HBV. Among patients with available data for C-P class (n=332), 132 (39.8%) patients had a documented C-P class in the EHR, and C-P class

Table 1 Demographics and Clinical Characteristics of Patients Who Initiated 1L Atezolizumab Plus Bevacizumab for uHCC in the US Oncology Network During the Study Identification Period

Variable	Overall (N = 374)	"Trial-Like" Subgroup (N = 132)[a]
Age (years) at index, n (%)		
Mean (SD)	68.8 (8.9)	69.5 (9.0)
Median (Min, Max)	68.8 (31.6–90+)	69.4 (31.6–88.0)
Age group at index, n (%)		
<65 years	115 (30.7)	31 (23.5)
≥65 years	259 (69.3)	101 (76.5)
Sex, n (%)		
Female	79 (21.1)	29 (22.0)
Male	295 (78.9)	103 (78.0)
Race/ethnicity, n (%)		
White, Non-Hispanic	181 (48.4)	72 (54.5)
Black, Non-Hispanic	41 (11.0)	13 (9.8)
Hispanic or Latino	24 (6.4)	7 (5.3)
Asian, Non-Hispanic	20 (5.3)	7 (5.3)
Other/Not documented	108 (28.9)	33 (25.0)

(*Continued*)

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Table 1 (Continued).

Variable	Overall (N = 374)	"Trial-Like" Subgroup (N = 132)[a]
Practice region, n (%)		
South	145 (38.8)	46 (34.8)
West	158 (42.2)	57 (43.2)
Midwest	59 (15.8)	26 (19.7)
Northeast	12 (3.2)	3 (2.3)
BMI category within 30 days of index, n (%)		
Non-obese (<30 kg/m^2)	254 (67.9)	87 (65.9)
Obese (≥30 kg/m^2)	100 (26.7)	37 (28.0)
Not documented	20 (5.3)	8 (6.1)
ECOG PS within 30 days of index, n (%)		
0	63 (16.8)	41 (31.1)
1	176 (47.1)	91 (68.9)
2	44 (11.8)	-
3+	8 (2.1)	-
Not documented	83 (22.2)	-
Comorbidities documented within 6 prior to index, n (%)		
Cardiac dysfunction	20 (5.3)	8 (6.1)
GI dysfunction	7 (1.9)	<5
Renal disease	41 (11.0)	16 (12.1)
Hypertension	201 (53.7)	70 (53.0)
Diabetes	134 (35.8)	49 (37.1)
Underlying liver disease[b], n (%)		
Cirrhosis	59 (15.8)	27 (20.5)
Hepatitis B virus (HBV)	28 (7.5)	9 (6.8)
Hepatitis C virus (HCV)	172 (46.0)	55 (41.7)
Non-alcoholic steatohepatitis (NASH)	27 (7.2)	14 (10.6)
Non-alcoholic fatty liver disease (NAFLD)	9 (2.4)	4 (3.0)
Alcohol-related liver disease	56 (15.0)	18 (13.6)
Other	<5	0
Unknown/not documented	112 (30.0)	50 (37.9)

(*Continued*)

Table 1 (Continued).

Variable	Overall (N = 374)	"Trial-Like" Subgroup (N = 132)[a]
Liver disease etiology[b], n (%)		
Viral[c]	192 (51.3)	61 (46.2)
Non-viral	70 (18.7)	25 (18.9)
Unknown/not documented	112 (30.0)	46 (34.8)
Extrahepatic metastatic sites (EHS), macrovascular invasion (MVI), or both[b], n (%)		
EHS only	88 (23.5)	34 (25.8)
MVI only	90 (24.1)	24 (18.2)
Both EHS and MVI	28 (7.5)	10 (7.6)
Neither EHS nor MVI	168 (45.0)	64 (48.5)
Location of extrahepatic metastatic sites[b], n (%)		
Bone	34 (9.1)	10 (7.6)
Brain	0	0
Lung	26 (7.0)	12 (9.1)
Lymph nodes	35 (9.4)	14 (10.6)
Pleura	<5	0
Other	31 (8.3)	10 (7.6)
Not documented	258 (69.0)	88 (66.7)
C-P class[d], n (%)		
Class A (5–6 points)	229 (61.2)	132 (100)
Class B (7–9 points)	91 (24.3)	-
Class C (10–15 points)	12 (3.2)	-
Not documented	42 (11.2)	-
ALBI grade[d], n (%)		
Grade 1 (≤ −2.60)	107 (28.6)	56 (42.4)
Grade 2 (> −2.60 to ≤ −1.39)	217 (58.0)	76 (57.6)
Grade 3 (> −1.39)	30 (8.0)	-
Not documented	20 (5.3)	-

Notes: [a]Patients in the "trial-like" subgroup had ECOG PS 0–1, C-P class A, and ALBI grade 1–2. [b]Prior to index date. [c]Viral etiology includes hepatitis B and/or hepatitis C alone or in combination with other non-viral underlying disease(s). [d]Within 90 days prior to the 1L initiation date or the earliest value after 1L initiation.

Abbreviations: 1L, first-line; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; C-P, Child-Pugh; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic metastatic sites; IQR, interquartile range; MVI, macrovascular invasion.

was derived for an additional 200 (60.2%) patients. As a result, there were 229 (61.2%), 91 (24.3%), and 12 (3.2%) patients from the overall sample with C-P class A, B, and C, respectively. There were 107 (28.6%) patients with ALBI grade 1, 217 (51.0%) with ALBI grade 2, and 30 (8.0%) with ALBI grade 3. Among patients with available data for

ALBI who were C-P class A (n=218), 77 (35.3%) were ALBI grade 1 and 136 (62.4%) patients were ALBI grade 2. The median (interquartile range [IQR]) duration of follow-up from initiation of 1L therapy was 5.6 (2.7–12.0) months.

Treatment Patterns

Prior treatment with locoregional therapies (LRT) was documented in 121 (32.4%) patients. Bevacizumab biosimilars were used in 333 (89.0%) patients, and 346 (92.5%) initiated bevacizumab on the same day as atezolizumab. Initiation of atezolizumab and bevacizumab on separate days but within 2 cycles was observed in 28 (7.5%) patients. Of 296 (79.1%) patients who discontinued 1L atezo-bev during the study period, the primary reason for discontinuation was disease progression or hospice (n=167, 44.7%). Additionally, 11 (2.9%) patients discontinued due to toxicity or an adverse event.

Additional treatment patterns are included in Table 2. Of the 296 patients who discontinued, only 55 (18.6%) patients proceeded to second-line therapy (2L). The most common 2L regimens included cabozantinib (n=21, 38.2%), lenvatinib (n=13, 23.6%), or sorafenib (n=9, 16.4%). Only 14 (3.7%) patients proceeded to 3L during the study period. Treatment sequencing from 1L to 3L is shown in Figure 1.

Table 2 Treatment Patterns of Patients Who Initiated 1L Atezolizumab Plus Bevacizumab for uHCC in the US Oncology Network During the Study Identification Period

Variable	Overall (N = 374)
Locoregional therapies (LRT) prior to the index date	
LRT type, n (%)	
Ablation	17 (4.5)
Transarterial embolization	7 (1.9)
Transarterial chemoembolization	57 (15.2)
Radioembolization	73 (19.5)
Not documented	253 (67.6)
LRT frequency, n (%)	
1	58 (15.5)
2	25 (6.7)
3+	38 (10.2)
Not documented	253 (67.6)
Esophagogastroduodenoscopy (EGD) procedures within 12 months prior to the index date	
Timing of latest EGD procedure, n (%)	
≤6 months prior to index	41 (11.0)
>6-≤12 months prior to index	7 (1.9)
Not documented	326 (87.2)
Time from latest EGD procedure to initiation of 1L systemic therapy (weeks)	
Patients with available data, N	48
Mean (SD)	11.2 (13.1)
Median (Min, Max)	6.4 (0.6–49.4)

(*Continued*)

Table 2 (Continued).

Variable	Overall (N = 374)
1L systemic therapy	
Bevacizumab type, n (%)	
Reference product	41 (11.0)
Biosimilar product	333 (89.0)
Bevacizumab administration, n (%)	
Same day as initiation of atezolizumab	346 (92.5)
Within 42 days of initiation of atezolizumab	28 (7.5)
Treatment disposition and reasons for discontinuation, n (%)	
Treatment ongoing	78 (20.9)
Treatment discontinued during the study observation period	293 (78.3)
Death	62 (16.6)
Hospice (excluding death)	78 (20.9)
Progression (excluding death or hospice)	89 (23.8)
One reason (excluding death, hospice, or progression)	51 (13.6)
Lost to follow-up	23 (6.1)
Adverse Event	11 (2.9)
Other	17 (4.5)
Multiple reasons (excluding death, hospice, or progression)	13 (3.5)
Reason not documented	3 (0.8)

Abbreviations: 1L, first-line; EGD, esophagogastroduodenoscopy; LRT, locoregional therapies.

Clinical Outcomes

During the follow-up period, 224 (59.9%) patients experienced a rwPFS event, and 163 (43.6%) died. Median (95% CI) rwPFS was 6.4 (5.1–7.7) months in the overall cohort and 9.4 (5.7–12.5) months in the "trial-like" subgroup (Figure 2). The estimated rwPFS was 52.2% (95% CI: 46.7–57.5%) at 6 months and 33.4% (95% CI: 27.8–39.1%) at 12 months for all patients (Figure 2). Median (95% CI) OS was 13.2 (9.5–15.9) months in the overall cohort and 16.5 (13.2–NR) months in the "trial-like" subgroup (Figure 3). The estimated OS was 68.6% (95% CI: 63.2–73.3%) at 6 months and 53.5% (95% CI: 47.4–59.2%) at 12 months for all patients (Figure 3).

Subgroup Analysis

Unadjusted median (95% CI) rwPFS and OS are reported by C-P class, ALBI grade, ECOG PS, liver disease etiology, and race/ethnicity category in Table 3. As expected, we observed differences in OS by the degree of liver dysfunction and ECOG performance status. Median (95% CI) OS among ALBI grades 1, 2 and 3 were 16.8 (13.8–NR), 9.9 (8.1–15.8), and 2.1 (1.3–4.5) months, respectively, and median (95% CI) OS among ECOG PS 0, 1, and ≥2 were 19.3 (13.8–NR), 9.9 (8.1–15.8), and 3.2 (2.2–6.5) months, respectively (P<0.0001 for both). Statistically significant differences were also observed in rwPFS by ALBI grade (P=0.002) and by ECOG PS (P<0.0001). While OS differed by C-P class (median [95% CI], C-P class A: 16.5 [12.6–NR], C-P class B: 7.5 [4.7–9.9], C-P class C: 4.5 [1.3–NR], P<0.0001), a significant

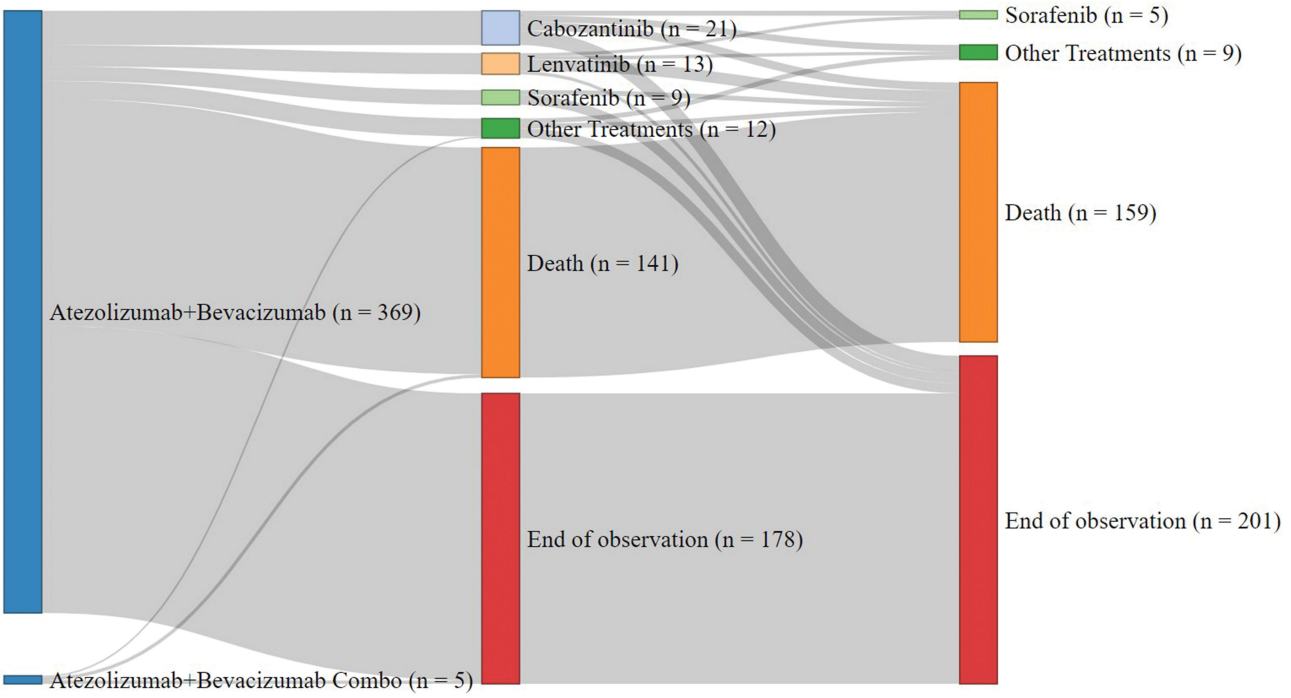


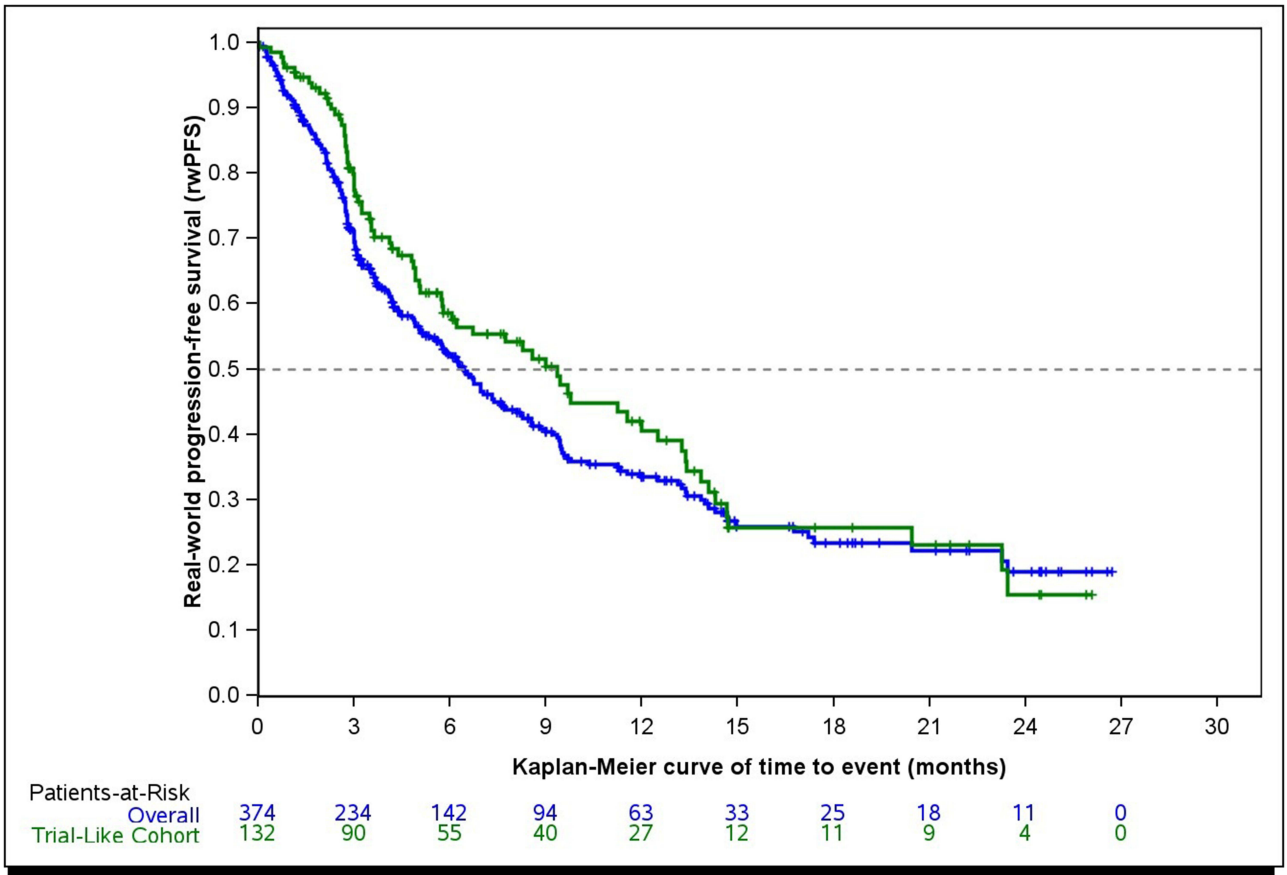
Figure 1 Treatment sequencing of patients who initiated 1L atezolizumab plus bevacizumab for uHCC in the US Oncology Network during the study identification period.
Notes: "End of observation" group includes patients who did not initiate a subsequent regimen and had no record of death during the observation period. Of the 178 patients in this group at 2L, n=78 had ongoing 1L therapy. An additional 23 patients did not initiate a subsequent regimen at 3L and had no record of death during the observation period. "Other treatments" in 2L included nivolumab ± ipilimumab, regorafenib, durvalumab, FOLFOX, pembrolizumab + lenvatinib, and ramucirumab.

difference in rwPFS by C-P class was not observed (P=0.19). Notably, there were no significant differences in rwPFS or OS by liver disease etiology (P=0.58, P=0.43, respectively) or by race and ethnicity (P=0.74, P=0.85, respectively).

Discussion

In this real-world study of patients who initiated 1L atezo-bev for uHCC at community oncology clinics in the United States, we found many patients had clinical features that would have excluded their participation in the IMbrave150 Trial, including over 1 in 4 patients with C-P class B/C cirrhosis and nearly 1 in 5 patients with ECOG PS 2 or more. Additionally, our real-world cohort had a higher proportion of elderly patients and racial ethnic minorities. Furthermore, real-world clinical practice may also vary from clinical trial protocols in terms of the timing and frequency of monitoring, adherence to treatment, management of complications, and measurement of clinical outcomes such as progression. Despite these differences, many of which could lead to less favorable results in the real-world study, patients had a median rwPFS of 6.4 months and OS of 13.2 months, respectively. Subgroup analyses showed that patients with negative prognostic factors such as greater liver dysfunction or poor performance status exhibited worse rwPFS and OS compared to those with preserved liver function and performance status. Differences in patient characteristics of the overall study cohort warranted further evaluation of outcomes among the sub-cohort of patients with trial-like characteristics. Indeed, among trial-like patients, the median rwPFS was 9.4 months and OS was 16.5 months, which is consistent with estimates from the IMbrave150 Trial. However, the trial-like cohort only considers a limited number of patient characteristics (ECOG PS, C-P class, ALBI grade) and other patient characteristics described in Table 1 could be different from the IMbrave150 Trial population. For example, the trial-like cohort consists of older patients (median age: 70 vs 64) and includes a higher proportion of patients with ALBI grade 2 (58% vs 43%) relative to the IMbrave150 trial population, suggesting that the real-world trial-like cohort may have a poorer prognosis.

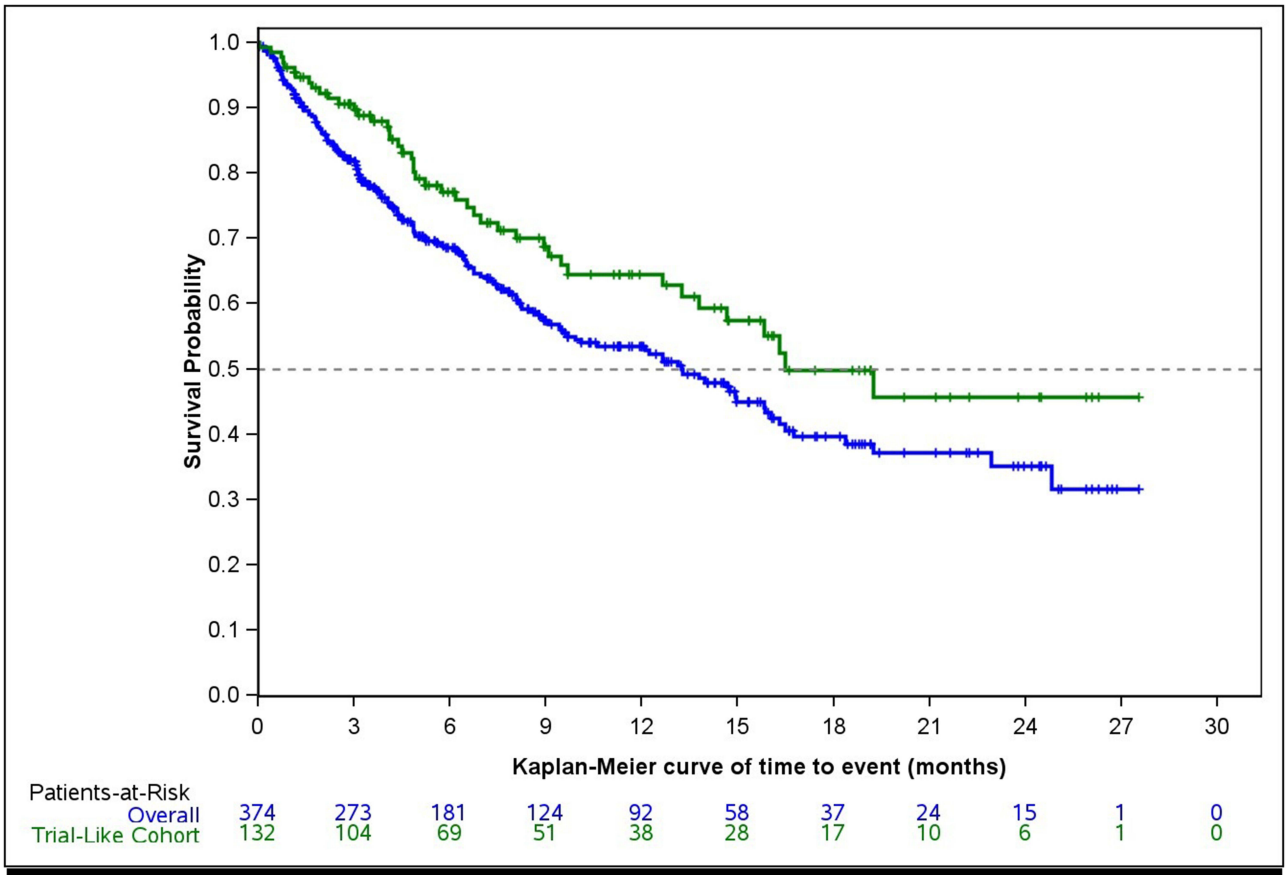
Findings from this real-world cohort of patients treated at community oncology practices align with results from other US-based studies conducted in other practice settings, including the Veteran Health Administration (VHA) and academic institutions. Using medical records from the National VHA data warehouse from 2017 to 2022, Kaplan et al (2024)



Variable	Overall (N = 374)	'Trial-Like' Cohort (N = 132)
Events, n (%)	224 (59.9)	74 (56.1)
Median (95% CI) rwPFS in months	6.4 (5.1–7.7)	9.4 (5.7–12.5)
IQR in months	2.7–17.2	3.3–20.4
rwPFS probability, % (95% CI)		
3 months	69.5 (64.4–74.0)	77.3 (68.9–83.8)
6 months	52.2 (46.7–57.5)	58.6 (48.9–67.1)
9 months	40.8 (35.2–46.4)	51.6 (41.6–60.7)
12 months	33.4 (27.8–39.1)	40.5 (30.3–50.5)
15 months	25.9 (20.3–31.9)	25.7 (16.2–36.2)
18 months	23.4 (17.7–29.5)	25.7 (16.2–36.2)
21 months	22.1 (16.4–28.4)	23.1 (13.7–33.9)
24 months	19.0 (12.9–26.0)	15.4 (6.4–28.0)

Figure 2 Kaplan-Meier analysis of median rwPFS for patients who initiated 1L atezolizumab plus bevacizumab for uHCC in the US Oncology Network during the study identification period.
Abbreviations: CI, confidence interval; IQR, interquartile range; rwPFS, real-world progression-free survival.

reported a median OS of 12.8 (95% CI: 10.6–17.1) months among veterans diagnosed with uHCC who received 1L A+B (N=405).[9] Storandt et al (2024) observed a median OS of 21.6 (95% CI: 17.7–34.9) months for patients with C-P class A (n=226) and 6.4 (95% CI: 5.2–9.0) months for those with C-P class B (n=86) treated at multiple academic institutions across the US.[10]



Variable	Overall (N = 374)	'Trial-Like' Cohort (N = 132)
Events, n (%)	163 (43.6)	44 (33.3)
Median (95% CI) OS in months	13.2 (9.5–15.9)	16.5 (13.2–NR)
IQR in months	4.1–NR	6.5–NR
OS probability, % (95% CI)		
3 months	81.8 (77.4–85.5)	89.8 (83.0–93.9)
6 months	68.6 (63.2–73.3)	77.1 (68.0–83.8)
9 months	57.4 (51.4–62.9)	68.7 (58.5–76.8)
12 months	53.5 (47.4–59.2)	64.5 (53.9–73.3)
15 months	45.0 (38.3–51.4)	57.4 (45.7–67.4)
18 months	39.6 (32.6–46.6)	49.8 (37.0–61.4)
21 months	37.1 (29.7–44.5)	45.7 (31.6–58.6)
24 months	35.2 (27.3–43.1)	45.7 (31.6–58.6)

Figure 3 Kaplan-Meier analysis of median OS for patients who initiated 1L atezolizumab plus bevacizumab for uHCC in the US Oncology Network during the study identification period.
Abbreviations: CI, confidence interval; IQR, interquartile range; NR, not reached; OS, overall survival.

The present findings are also generally consistent with the results of other observational studies conducted globally including countries outside of the US, though some differences may arise due to regional variations in clinical practice, health systems, and patient populations. For example, D'Alessio et al (2022) conducted a global multi-center retrospective study of A+B patients with uHCC across seven countries, including the US, reporting a median OS of 14.9 (95%

Table 3 Subgroup Analysis of Unadjusted rwPFS and OS for Patients Who Initiated 1L Atezolizumab Plus Bevacizumab for uHCC in the US Oncology Network During the Study Identification Period

Variable	N	rwPFS		OS	
C-P class					
A	229	7.3 (5.4–9.4)	P=0.1902	16.5 (12.6–NR)	P<0.0001
B	91	5.7 (3.1–7.0)		7.5 (4.7–9.9)	
C	12	4.5 (1.3–9.2)		4.5 (1.3–NR)	
n/a	42	6.7 (2.6–17.4)		16.0 (8.7–NR)	
ALBI grade					
1	107	9.0 (5.8–12.5)	P=0.0024	16.8 (13.8–NR)	P<0.0001
2	217	6.4 (4.3–8.1)		9.9 (8.1–15.8)	
3	30	2.1 (1.3–4.5)		2.1 (1.3–4.5)	
n/a	20	6.2 (0.7–10.3)		16.0 (7.3–NR)	
ECOG PS					
0	63	8.5 (4.8–13.4)	P<0.0001	19.3 (13.8–NR)	P<0.0001
1	176	6.3 (4.9–9.4)		9.9 (8.1–15.8)	
2+	52	2.8 (1.6–4.2)		3.2 (2.2–6.5)	
n/a	83	7.0 (5.4–11.3)		24.8 (9.4–NR)	
Liver disease etiology					
Viral	192	6.7 (4.9–8.6)	P=0.5881	13.3 (8.9–18.4)	P=0.432
Non-viral	70	6.2 (4.3–9.5)		9.1 (6.2–19.3)	
n/a	112	6.4 (3.5–9.0)		16.0 (7.9–22.9)	
Race/Ethnicity					
White, NH	181	6.2 (4.3–8.6)	P=0.7435	10.6 (8.2–22.9)	P=0.8542
Black, NH	41	6.4 (3.1–13.2)		14.9 (7.0–NR)	
Hispanic	24	4.9 (2.6–8.5)		14.8 (7.1–NR)	
Asian, NH	20	5.6 (2.6–14.9)		14.9 (5.6–NR)	
Other or n/a	108	6.7 (4.5–9.4)		12.6 (8.7–16.8)	

Notes: Results are reported as median (95% CI), logrank p-value.
Abbreviations: ALBI, albumin-bilirubin; C-P, Child-Pugh; ECOG PS, Eastern Cooperative Oncology Group performance status; n/a, not documented; NR, not reached; NH, non-Hispanic.

CI: 13.6–16.3) months and a median PFS of 6.8 (95% CI: 5.2–8.5) months for all patients (n=216).[11] Allaire et al (2024) conducted a registry-based study in France and reported a median PFS of 5 months and a median OS of 23.7 months in a large prospective multicentric cohort (n=545).[12] Additionally, Himmelsbach et al (2022) reported a median PFS of 6.5 months in 66 patients with advanced HCC treated with 1L atezo-bev at four cancer centers in Germany and Austria between December 2018 and August 2021.[13] De Castro et al (2022) reported median (95% CI) PFS of 5.1 (2.6–7.6) months in 147 patients with advanced HCC who received atezo-bev regardless of prior treatment across six hospitals in Germany and Austria.[14] In the subgroup of patients (n=74) with C-P class A, ECOG PS 0–1, and no prior systemic

therapy for HCC, median (95% CI) PFS was 8.7 (5.9–11.5) months.[14] Lastly, Fulgenzi et al (2022) observed median (95% CI) PFS of 6.9 (6.1–8.3 months) in 296 patients with uHCC, C-P class A, and ECOG PS 0–1 who received 1L atezo-bev at one of 14 tertiary care centers across the USA, Europe and Asia.[15] The observed associations between C-P class, ALBI grade, and ECOG PS on clinical outcomes are expected given their prognostic nature and not unique to atezo-bev. Prior studies have demonstrated similar findings across 1L treatment regimens.[9–18]

Overall, these data underscore the importance of careful patient selection to achieve optimal safety and effectiveness. However, many patients in clinical practice present with greater liver dysfunction and worse performance status, and there are no proven therapies in this patient population. There is currently an ongoing prospective study to generate robust safety and efficacy estimates for atezo-bev in patients with C-P B cirrhosis.[19] However, real-world data is helpful to guide decision making and patient discussions about expectation in the interim. The poor observed outcomes in patients with Child Pugh class C cirrhosis or ALBI grade 3, with median survival less than 6 months in both subgroups, reinforce that these patients may be better suited for best supportive care given the high competing risk of mortality from their underlying liver disease.

There has been controversy about the efficacy of immunotherapy in patients with non-viral liver disease, postulated to be driven by T cell exhaustion in patients with MASLD.[20] While subgroup analysis of the IMbrave150 Trial suggested differential effect, lack of stratification by etiology precluded robust conclusions. Further, a post-hoc analysis found no significant difference in efficacy after adjusting for baseline differences in the groups.[21] While some prior real-world studies have found viral hepatitis treated with 1L atezo-bev to be associated with a more favorable PFS and OS relative to non-viral disease, most have found 1L atezo-bev to be effective regardless of etiology.[9–15,22,23] In this study, there was no association between clinical outcomes and etiology observed.

Previous studies have reported racial, ethnic and socioeconomic disparities in the incidence, treatment and outcomes of patients with HCC.[24,25] Racial minorities are often under-represented in clinical trials and may face barriers to timely detection and treatment including financial toxicity, transportation, language barriers, medical mistrust and other patient preferences that may impede treatment.[26,27] Therefore, real-world data are critical for understanding treatment practices and outcomes in diverse cohorts. While outcomes in our study did not appear to differ significantly across racial and ethnic subgroups as evidenced by overlapping confidence intervals, the sample size may be too small to draw definitive conclusions. It is also likely that patients in this study cohort were engaged in care at community oncology practices which does not exclude the possibility of upstream disparities in access to clinical care.

This study is subject to several limitations inherent to the nature of observational study designs. As this was a retrospective, observational study of EHR data, there is a risk of measurement bias as well as missing data. For instance, Vp classification of macrovascular invasion was not available for the analysis as it was not documented in charts within these US community oncology settings. Documentation of locoregional therapies and esophagogastroduodenoscopy was also limited as services performed outside of the network were not always recorded within the community oncology charts. While C-P class was captured as documented in the EHR in patients with available data, other patients' C-P class was derived from individual inputs which could include post-treatment data and therefore may not be representative of the patient's baseline status. Also, our study had a relatively short duration of follow-up, which precluded robust estimates of long-term survival. For the evaluation of rwPFS, this real-world study used provider-documented tumor assessments which may differ from the RECIST criteria used for PFS in clinical trials. Additionally, subgroup analyses of clinical outcomes were not statistically powered to study the differences across subgroups. Lastly, the patient characteristics, disease etiology, treatment patterns and outcomes are reflective of the US community oncology setting which may be different than those observed in academic and/or non-US settings. Despite these limitations, our study adds important effectiveness data from a well characterized set of patients treated in US oncology practices.

Conclusion

In US community oncology settings, atezo-bev is used as 1L treatment for uHCC in a broad and diverse patient population, including those with liver dysfunction, impaired performance status, and racial and ethnic minorities. Our real-world study provides further evidence to support the effectiveness of 1L atezo-bev for uHCC in appropriately selected patients. Among patients with similar clinical characteristics as those included in the IMbrave150 Trial, real-world clinical effectiveness appears similar to that reported from the clinical trial. While further research with larger

sample sizes and longer follow-up is warranted, findings from this study can help guide patient selection of appropriate treatment candidates and maximize the benefits of atezo-bev in clinical practice.

Ethics Statement

Institutional Review Board and Compliance/Privacy approval was gained prior to initiation of the retrospective research. Since this project involved the analysis of existing data and records, study information was analyzed in such a manner that research participants could not be directly identified. Patient informed consent was not required due to the nature of the study design. Thus, exemption status and a waiver of informed consent were approved by The US Oncology, Inc. Institutional Review Board. Data were handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA), the Health Information Technology for Economic and Clinical Health (HITECH) Act, and the Declaration of Helsinki.

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