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ORIGINAL ARTICLE

Atezolizumab plus bevacizumab as first-line treatment of unresectable hepatocellular carcinoma: interim analysis results from the phase IIIb AMETHISTA trial

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Background: The treatment of advanced hepatocellular carcinoma (HCC) with atezolizumab and bevacizumab led to significant improvements in overall survival (OS), progression-free survival (PFS), and response rate compared with sorafenib in the phase III IMbrave150 trial. The etiology of background liver disease can differ between Eastern and Western populations, leading to a potentially different impact of systemic therapies; therefore the unequal representation must be considered in the IMbrave150 trial. To provide further data on the safety and effectiveness of atezolizumab and bevacizumab, the phase IIIb AMETHISTA (Atezolizumab plus bevacizumab in METastatic HCC Italian Safety TriAl) ran in a Western (Italian) population of patients with advanced HCC. The results of the interim analysis are presented in this paper.

Methods: AMETHISTA is a multicenter, phase IIIb, single-arm study evaluating the safety and effectiveness of atezolizumab and bevacizumab in an Italian population of patients with systemic treatment-naive HCC (ClinicalTrials.gov: NCT04487067). The primary objective was safety (incidence of grade 3-5 bleeding/hemorrhages). The main secondary objective was effectiveness.

Results: A total of 152 patients were enrolled and 149 were treated. At the cut-off date, the median observation time was 13.4 months (interquartile range 8.3-15.5 months). The incidence of grade 3-5 bleeding/hemorrhages was 11.4%. Besides, results of other safety endpoints were consistent with the safety profile of atezolizumab plus bevacizumab, and the underlying disease, without any new safety observation. The median OS was 18.2 months (95% confidence interval 15.4 months to not evaluable); the median PFS was 8.5 months (95% confidence interval 7.5-11.2 months).

Conclusion: Results from the interim analysis are consistent with data from the IMbrave150 trial, and further confirm first-line atezolizumab plus bevacizumab as a standard of care for patients with systemic treatment-naive advanced and unresectable HCC.

Key words: hepatocellular carcinoma, HCC, bevacizumab, atezolizumab, immune checkpoint inhibitors

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents ∼90% of primary liver cancers.[1] For individuals with unresectable advanced HCC who are not eligible for surgical and locoregional treatments, the oral multikinase inhibitor sorafenib was the first and only systemic treatment for more than a decade.[2-5] More recently, other compounds have been approved as the first-line (lenvatinib) or second-line (regorafenib, cabozantinib, and ramucirumab) treatments.[6-9] However, the narrow therapeutic window and the high rate of progression constitute major pitfalls of these therapies.

Strong scientific rationale and emerging clinical data suggest that the immunotherapy—anti-angiogenic combination strategy providing vascular endothelial growth factor (VEGF) and programmed death-ligand 1 (PD-L1) blockade may be clinically beneficial in a number of tumor types, including HCC.[10,11] Accordingly, the combination of atezolizumab, an immune checkpoint inhibitor that targets PD-L1 protein, and bevacizumab, a monoclonal antibody that targets VEGF, was investigated in the treatment of advanced HCC. This combination showed positive results in early clinical trials, and, subsequently, in the randomized phase III IMbrave150 trial, which demonstrated a significant improvement in overall survival (OS), progression-free survival (PFS), and response rates compared with sorafenib in patients with advanced HCC; all patients underwent esophagogastroduodenoscopy (EGD) before treatment start for the management of varices, if clinically relevant.[12,13] The positive results of this trial established atezolizumab plus bevacizumab as a standard of care for unresectable HCC.

Combinations of PD-L1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors have also been evaluated in this setting. In particular, the infusion regimen termed STRIDE, composed of durvalumab (anti-PD-L1) combined with a high priming dose of tremelimumab (anti-CTLA-4), significantly improved OS versus sorafenib in the open-label, phase III HIMALAYA trial, representing an additional first-line option for patients with unresectable HCC.[14,15] In addition, the combination of nivolumab [programmed cell death protein 1 (PD-1) inhibitor] and ipilimumab (anti-CTLA-4) showed in the CheckMate 9DW study a statistically significant improvement in OS and response rates compared with sorafenib or lenvatinib.[16] However, it was associated with a higher risk of immune-related adverse effects, necessitating careful patient selection and monitoring.

Based on the results of the IMbrave150 trial, the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMA) approved the atezolizumab plus bevacizumab combination in May and October 2020, respectively, for the treatment of patients with advanced or unresectable HCC who have not received previous systemic therapy.[17-19] In June 2022, the combination treatment has been granted reimbursement by the Italian Medicines Agency (AIFA).

With regard to the safety profile of the combination, the use of bevacizumab has been associated with an increased risk of bleeding events; in clinical trials across all indications, the overall incidence of the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (NCI-CTCAE version 3) grade 3-5 bleeding reactions ranges from 0.4% to 6.9%.[20] In particular, in the IMbrave150 trial, at a median follow-up of 8.9 months, incidence rates of 6.4% and 1.5% were reported for grade 3-4 and grade 5 bleeding events.[14] Of note, the cumulative risk increases with treatment duration, and, at the subsequent median follow-up of 15.6 months, the incidence of grade 3-4 bleeding events was 9.0% and that of grade 5 bleeding events was 1.8%.[21]

With regard to the etiology of background liver disease, this can differ between Eastern and Western populations, leading to a potential different impact on the safety and efficacy of systemic therapies; therefore the unequal representation must be considered in the IMbrave150 trial. Moreover, retrospective studies may only report fewer details of adverse events, especially when not severe. All studies available so far on the safety and efficacy of atezolizumab plus bevacizumab for HCC, besides the IMbrave150, have been retrospective.[22-24]

To further evaluate the safety and effectiveness profile of the combination treatment in patients with advanced HCC, a prospective, multicenter, phase IIIb, single-arm study of atezolizumab in combination with bevacizumab [Atezolizumab plus bevacizumab in METastatic HCC Italian Safety TriAl (AMETHISTA study)] was set up in a Western (Italian) population of patients with unresectable HCC. To promptly share the first results, and allow physicians to make the choices most tailored to individual patients, the protocol was amended to provide an interim analysis. The data cut-off was 17 June 2022, ∼10 months after the end of enrollment. The results of the interim analysis are presented in this paper.

PATIENTS AND METHODS

Study design and setting

AMETHISTA is a prospective, open-label, single-arm, phase IIIb trial that started in August 2020 among 21 Italian oncology and gastroenterology centers. The trial evaluates the safety and effectiveness of atezolizumab plus bevacizumab in patients with unresectable HCC not previously treated with systemic therapy. The interim analysis has been conducted at the data cut-off of 17 June 2022, ∼10 months after the end of enrollment (12 August 2021), in line with the IMbrave150 trial. The study was completed on August 13, 2024. The AMETHISTA trial included adult patients (≥18 years of age) with histologically confirmed HCC, diagnosed via biopsy within 6 months before recruitment. Patients were ineligible for surgery and/or locoregional therapies or had progressive disease following such treatments. In addition, they were not suitable for further locoregional therapies,

including transarterial chemoembolization (TACE), had no prior systemic therapy, and presented with at least one measurable (per RECIST 1.1) untreated lesion. Eligibility criteria also required an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, Child—Pugh class A, and adequate hematologic and end-organ function. All patients had to have an EGD within 6 months before treatment. If present, participating investigators were recommended to treat esophageal varices according to local standards of care before enrollment. No specific exclusion criteria according to the size of varices were settled. All sizes of varices have to be assessed and treated before enrollment according to local standard of care. A full list of inclusion criteria is provided in Supplementary Material S1, available at https://doi.org/10.1016/j.esmoop.2024.104110. Among the key exclusion criteria, there was a history of autoimmune disease, leptomeningeal disease, brain metastases, major pulmonary conditions, major cardiovascular disease, and malignancies other than HCC within 5 years before screening.

The study was carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and the study protocol was approved by the Independent Ethics Committee at each site and by the Italian Health Authority. All patients signed an informed consent form. This study is registered with ClinicalTrials.gov (registration number NCT04487067).

Treatment and procedures

Atezolizumab 1200 mg and bevacizumab 15 mg/kg were administered intravenously every 3 weeks until unacceptable toxicity, or loss of clinical benefit (determined after an integrated assessment of radiographic, biochemical data, and clinical status), or patient refusal. In case of disease progression, the continuation of combination treatment was allowed in the presence of all the following criteria: evidence of clinical benefit, as determined by the investigator following a review of all available data; absence of symptoms and signs (including laboratory values) indicating unequivocal progression of disease; absence of a decline in ECOG performance status that can be attributed to disease progression; and absence of tumor progression at critical anatomical sites (e.g. leptomeningeal disease or brain metastases) that protocol-allowed medical interventions cannot manage. If one component of the study treatment (atezolizumab, or bevacizumab) was permanently discontinued because of tolerability concerns, the patient might continue with the other drug as per protocol.

Study measures

The primary objective was the safety of atezolizumab plus bevacizumab in terms of incidence of grade 3-5 bleeding/hemorrhages graded per the NCI CTCAE version 5.0. The number of patient-years at risk of events, the annual bleeding rate, the median time to onset, and the resolution of any-grade bleeding were also calculated. The annual bleeding rate was calculated considering the total number of grade 3-5 bleeding events (including multiple occurrences per patient, if any) and the total number of patient-years 'at risk of event' under observation. Additional information about the management of patients with grade 5 bleeding/hemorrhage events was reported (see Supplementary Material S1, available at https://doi.org/10.1016/j.esmoop.2024.104110). Comprehensive details on bleeding events among patients with esophageal varices versus those without, prior variceal management, history of bleeding episodes, and whether bevacizumab was discontinued will be provided in the final analysis. Other secondary safety endpoints were the incidence and severity of treatment-emergent adverse events (TEAEs), with severity determined according to NCI CTCAE version 5.0, vital signs, and clinical laboratory test results. Any TEAEs, serious TEAEs, fatal TEAEs, immune-mediated TEAEs (imTEAEs, i.e. TEAEs treated with corticosteroids or immunosuppressant drugs), and AEs of special interest (AESI) were considered. TEAEs were defined as AEs with an onset date on or after the start of the first study treatment component. TEAEs were reported by System Organ Class and Preferred Term according to MedDRA thesaurus terms. The full list of considered AESI is provided in Supplementary Material S1, available at https://doi.org/10.1016/j.esmoop.2024.104110. AESI included the suspected transmission of an infectious agent by the study treatment (STIAMP).

The main secondary objective was the effectiveness of atezolizumab plus bevacizumab assessed in terms of OS, defined as the time from initiation of study treatment to death from any cause. Other secondary endpoints were PFS, defined as the time from initiation of study treatment to the first occurrence of disease progression, or death from any cause (whichever occurs first); time to progression (TTP), defined as the time from initiation of study treatment to the first occurrence of disease progression; postprogression survival (PPS), defined as the time from the first occurrence of disease progression to death from any cause; objective response rate (ORR), defined as a complete or partial response, as determined by the investigator according to RECIST version 1.1 criteria; duration of response, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first); number/rate of patients starting second or further lines of treatment; evaluation of patient-reported outcomes using National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

The exploratory endpoints of the AMETHISTA trial were OS and PPS based on predefined patterns of progression (growth versus new lesion or intrahepatic versus extrahepatic); OS based on type and duration of each poststudy treatment; and OS based on predefined reasons for treatment withdrawal. Exploratory biomarker and economic analyses were also planned. In this paper, the interim analysis of primary, main secondary, and other secondary endpoints (PFS, TTP, PPS, and ORR) is presented. Other secondary and exploratory endpoints will be addressed in future analyses.

Statistical analysis

The sample size was determined according to a sample of convenience, as defined by Lohr,[25] and was estimated according to the purpose of obtaining a reliable evaluation of the incidence of grade 3-5 bleeding/hemorrhages in a Western population of patients treated with atezolizumab plus bevacizumab. Continuous data were summarized with mean, standard deviation (SD), median, interquartile range, and range. Categorical data were presented by absolute and relative frequencies or contingency tables. OS, PFS, TTP, PPS, and duration of response were analyzed using the Kaplan–Meier product-limit method with Greenwood's formula and descriptive statistics. The estimated median and the quartiles were provided together with a corresponding two-sided 95% confidence interval (95% CI). Moreover, the Kaplan–Meier curve with a 95% CI was presented. ORR was summarized as the percentage of patients who had a complete response or partial response as the best response before any evidence of progression. A 95% CI was derived using Wilson score intervals.

Safety analyses were conducted in the 'safety set', including all enrolled patients who had at least one administration of atezolizumab plus bevacizumab. Analyses of other outcomes were conducted in the intent-to-treat (ITT) set, including all enrolled patients.

RESULTS

Study population

Overall, 210 patients were screened for inclusion; 152 patients (ITT) were enrolled and 149 were treated. Treated patients were males in 79.2% of cases ($n = 118$) and the median age was 69 years (range 43-86 years). Baseline characteristics of treated patients are summarized in Table 1. Hepatitis C was the most commonly reported etiology (43.0%, $n = 64$), followed by alcohol (26.2%, $n = 39$). Further details on etiology are reported in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.104110. Most of the patients were in Barcelona Clinic Liver Cancer (BCLC) stage C (65.1%, $n = 97$).

Patients with varices at baseline (32 patients, 21.5%) were treated with banding (3 patients, 2.0%), non-cardioselective beta-blockers (7 patients, 4.7%), or other treatments not specified (1 patient, 0.7%). At baseline, 54 patients (36.2%) received a prior locoregional therapy: intra-arterial treatments (TACE; drug-eluting bead TACE, transarterial embolization) had been carried out in 43 patients (28.9%), radiofrequency ablation in 16 (10.7%), transarterial radioembolization in 11 patients (7.4%); some patients received more than one type of locoregional therapy.

Table 1. Patients' demographic, and baseline characteristics ($n = 149$)

Characteristics	Values, *n* (%)
Age (years), median (range)	69 (43-86)
Males	118 (79.2)
Etiology[a]:	
• Hepatitis C	64 (43.0)
• Alcohol	39 (26.2)
• Hepatitis B	32 (21.5)
• Other[b]	21 (14.1)
ECOG PS score:	
• 0	126 (84.6)
• 1	23 (15.4)
BCLC stage:	
• Stage A	4 (2.7)
• Stage B	48 (32.2)
• Stage C	97 (65.1)
Presence of extrahepatic spread	62 (41.6)
Presence of macrovascular invasion	29 (19.5)
Cirrhosis	42 (28.2)
Modified albumin-bilirubin grade[c]:	
• Grade 1	77 (51.7)
• Grade 2a	31 (20.8)
• Grade 2b	30 (20.1)
• Grade 3	0 (0)
Presence of varices[d]:	32 (21.5)
• Treated[e]	11 (7.4)[f]
• With concomitant macrovascular invasion	11 (7.4)[f]
Prior locoregional therapy[g]	54 (36.2)
Prior surgery	53 (35.6)
Alpha-fetoprotein ≥400 ng/ml	43 (28.9)

BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]More than one etiology can be reported for each patient.
[b]Other: nonalcoholic, non-hepatitis C virus/hepatitis B virus etiology.
[c]Data were available for 138 patients.
[d]Grade of varices was not collected.
[e]Before enrollment, according to the local standard of care.
[f]34.4% of patients with varices.
[g]More than one therapy can be reported for each patient.

Patients' disposition and exposure

At the cut-off date, 50 patients (32.9% of ITT) were on treatment and 99 (65.1%) had permanently discontinued treatment. Eighty-four patients (55.3%) started the follow-up, 36 (23.7% of ITT) of which were still in follow-up at the cut-off date, while 48 (31.6% of ITT) had discontinued the follow-up. Fifteen patients (9.9%) did not return to follow-up visits. Sixty-three patients (41.5%) discontinued the study. Full details of patients' disposition and follow-up definition are provided in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.104110.

The mean (SD) extent of exposure to atezolizumab was 8.5 (5.7) months (median 8.3 months, range 0-21 months) and the mean (SD) number of cycles of atezolizumab was 12.3 (7.8; median 12.0, range 1-31). The mean (SD) extent of exposure to bevacizumab was 7.8 (5.5) months (median 7.3 months, range 0-21 months) and the mean (SD) number of cycles of bevacizumab was 10.9 (7.2; median 11.0, range 1-31).

Safety results

At the cut-off date, the median observation time was 13.4 months [interquartile range 8.3-15.5 months; mean (SD) 12.1 (5.1) months].

A total of 60 any-grade bleeding events, most of them low grade, were reported in 46 patients (30.9%) and mainly involved the respiratory (12.8% of patients; of these, only one reported hemoptysis grade 3) and the gastrointestinal (12.1% of patients; of these, 13 reported grade ≥3 events) tract.

A total of 21 grade 3-5 bleeding/hemorrhage events occurred in 17 patients (11.4%). Grade 3-4 bleeding/hemorrhage events were reported in 14 patients (9.4%), considering the maximum toxicity grade. There were three grade 5 bleeding/hemorrhage events (2.0%; one case of shock hemorrhagic following two gastrointestinal bleeding events, one case of small intestinal hemorrhage, and one of upper gastrointestinal hemorrhage), two of which were deemed related to bevacizumab (Tables 2 and 3; see Supplementary Material S1, available at https://doi.org/10.1016/j.esmoop.2024.104110 for narratives of the three cases). None of the grade 5 bleeding events were evaluated by the investigator as related to atezolizumab (Table 2). The most common grade 3-5 bleeding/hemorrhage events are summarized in Table 3.

The number of patient-years at risk of events (i.e. grade 3-5 treatment-emergent bleeding/hemorrhage) was 154.2, and the annual bleeding/hemorrhage rate was 0.14 (95% CI 0.08-0.21).

The median time to onset of first any-grade bleeding events was 100 days (range 49.0-226.0 days) and 109 days (range 5.0-298.0 days) with regard to grade ≥3 events. The median time to resolution of any-grade bleeding events was 11 days (range 4.0-35.0 days).

Among the 11 patients with treated varices, 6 (54.5%) reported nine grade ≥3 bleeding events (five grade 3 events, two grade 4 events, and two fatal events). Three of them were reported as related to bevacizumab only, one to atezolizumab only, and one event was related to both drugs. Fatal events were not reported as related to any drug. Among the 21 patients reporting nontreated varices, 8 (38.1%) reported 10 bleeding events, of whom four were grade ≥3 (three grade 3 events and one fatal event). None of them was reported as related to any drug. Overall, among 32 patients with varices, the three fatal events were not reported as related to any drug.

Among the 11 patients with varices and concomitant macrovascular invasion (MVI) at baseline, 6 (54.5%) reported bleeding events, which were grade ≥3 in 4 patients (36.4%). Among the 21 patients with varices and without MVI, 8 (38.1%) patients reported bleeding events, which were grade ≥3 in 6 (28.6%) cases.

TEAEs by preferred term. In the safety population, any-grade TEAEs were reported in 143 patients (96.0%) and were related to any treatment in 106 patients (71.1%; Table 4). All-cause grade 3-4 TEAEs occurred in 90 patients (60.4%; Table 4). Treatment-related grade 3-4 events occurred in 60 patients (40.3%).

A total of 90 serious TEAEs were reported in 53 patients (35.6%; Table 4): 35 serious TEAEs in 27 patients (18.1%) were related to any treatment component, 9 serious TEAEs in 8 (5.4%) patients were related to atezolizumab, 32 serious TEAEs in 24 patients (16.1%) were related to bevacizumab, and 6 serious TEAEs in 5 (3.4%) patients were related to both atezolizumab and bevacizumab.

Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.104110, shows the most common treatment-related TEAEs, with details on grade 3-4 TEAEs, serious TEAEs, and treatment-related serious TEAEs.

Fourteen grade 5 TEAEs occurred in 14 (9.4%) patients (Table 4). None of these fatal TEAEs was considered related

Table 2. Overall incidence of bleeding/hemorrhage events and relationship with treatments

Bleeding/hemorrhage event	Overall, *n* (%)	Related to atezolizumab, *n* (%)	Related to bevacizumab, *n* (%)	Related to both, *n* (%)
Any grade	46 (30.9)	5 (3.4)	30 (20.1)	4 (2.7)
Grade 3-4[a]	14 (9.4)	1 (0.7)[b]	8 (5.4)	—
Grade 5[a]	3 (2.0)	—	2 (1.3)	—

n= number of patients.
[a]Each patient has been counted once based on maximum toxicity grade.
[b]Due to purpura, grade 3.

Table 3. Overall incidence of grade 3-5 bleeding/hemorrhage events by Medical Dictionary for Regulatory Activities (MedDRA) system organ class/preferred term[a]

Bleeding/hemorrhage events by MedDRA System organ class/preferred term	Values, *n* (%)/event
Gastrointestinal disorders	**13 (8.7)/16**
• Gastric hemorrhage	1 (0.7)/1
• Gastrointestinal hemorrhage	2 (1.3)/2
• Hematemesis	1 (0.7)/1
• Hemoperitoneum	1 (0.7)/1
• Large intestinal hemorrhage	1 (0.7)/1
• Melena	2 (1.3)/2
• Esophageal varices hemorrhage	2 (1.3)/2
• Pancreatic hemorrhage	1 (0.7)/1
• Rectal hemorrhage	1 (0.7)/1
• Small intestinal hemorrhage	1 (0.7)/1
• Upper gastrointestinal hemorrhage	2 (1.3)/3
Respiratory, thoracic, and mediastinal disorders	**1 (0.7)/1**
• Hemoptysis	1 (0.7)/1
Skin and subcutaneous tissue disorders	**1 (0.7)/1**
• Purpura	1 (0.7)/1
Vascular disorders	**3 (2.0)/3**
• Hemorrhage	2 (1.3)/2
• Hemorrhagic shock	1 (0.7)/1

[a]Each patient could have more than one event and is counted once for each preferred term.

Table 4. Overall incidence of TEAEs, serious, and fatal TEAEs; TEAEs of special interest; and relationship with treatments

Adverse events	Overall, *n* (%)	Related to atezolizumab, *n* (%)	Related to bevacizumab, *n* (%)	Related to both, *n* (%)
Any grade TEAEs	143 (96.0)	86 (57.7)	91 (61.1)	51 (34.2)
Grade 3-4 TEAEs	90 (60.4)	27 (18.1)[a]	46 (30.9)	11 (7.4)[a]
Serious TEAEs	53 (35.6)	8 (5.4)	24 (16.1)	5 (3.4)
Fatal TEAEs	14 (9.4)	—	3 (2.0)	—
AESIs	57 (38.3)	15 (10.1)	35 (23.5)	4 (2.7)
Grade 3-4 AESI	49 (32.9)	10 (6.7)[a]	32 (21.5)	3 (2.0)[a]
Fatal AESI	4 (2.7)	—	3 (2.0)	—

AESI, adverse events of special interest; TEAEs, treatment-emergent adverse events.
n= number of patients.
[a]The maximum reported toxicity grade was 3.

to atezolizumab and three were considered related to bevacizumab (shock hemorrhagic event, enterovesical fistula, and small intestinal hemorrhage). Fatal cases not related to any study drug were coronavirus disease-19 (COVID-19), cholangitis infective, bradycardia, pneumonia, death (unexplained), sepsis, COVID-19 pneumonia, upper gastrointestinal hemorrhage, ascites, each in one patient; and two cases of renal failure.

A total of 37 imTEAEs were reported in 23 (15.4%) patients. The most common were aspartate aminotransferase (AST) increase (four events) and arthralgia (three events), both in 3 (2.0%) patients. A total of nine imTEAEs grade 3-4 were reported in 9 (6.0%) patients. TEAEs suggestive of a potential drug-induced liver injury were reported in 29 patients (19.5%). The most common were transaminases increase [reported as AST increase, 11 events in 9 (6.0%) patients; alanine aminotransferase (ALT) increase, six events in 5 (3.4%) patients; hypertransaminasemia, 13 events in 10 (6.7%) patients], and hyperbilirubinemia [11 events in 8 (5.4%) patients]. None of these were reported by the investigator as a case of potential drug-induced liver injury according to Hy's law, defined as elevated ALT or AST ($>3\times$ baseline value) in combination with either elevated total bilirubin ($>2\times$ upper limit of normal) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia.[26]

A total of 86 AESIs were reported in 57 patients (38.3%; Table 4). Thirty-four serious AESI occurred in 27 patients (18.1%) and 24 of them in 19 patients were related to any study treatment component. The most commonly reported AESI was hypertension in 17 patients (11.4%). Seventy-two grade 3-4 AESIs were reported in 49 (32.9%) patients, and 49 grade 3 or 4 AESIs in 38 (25.5%) patients were related to any study treatment component (Table 4). Four AESIs in 4 (2.7%) patients were fatal, and three of them in 3 (2.0%) patients were related to bevacizumab (Table 4). No AESI was related to a suspected transmission of an infectious agent by the study treatment in any patient. TEAEs leading to permanent discontinuation of any study treatment were 59, and occurred in 44 (29.5%) patients; 36 events in 30 (20.1%) patients led to the permanent discontinuation of both treatments (Table 5).

An exploratory analysis of safety in the BCLC B population is reported in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.104110.

Vital signs and clinical laboratory test results. There were no important changes from screening to any postbaseline timepoint (including times of postinfusion) in mean and median values of weight, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and temperature. Similarly, there were no important changes from screening to any postbaseline timepoint in hematology, chemistry, and urine analyses.

OS and other time-to-event outcomes

At the cut-off date, the median OS was 18.2 months (95% CI 15.4 months to not evaluable; Figure 1A). The median PFS was 8.5 months (95% CI 7.5-11.2 months; Figure 1B). The median TTP was 10.8 months (95% CI 8.2-15.7 months; Figure 1C). Seventy-three patients were evaluated for PPS, which was 9.1 months (95% CI 7.3-13.8 months; Figure 1D).

ORR is presented in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.104110. Overall, 41 patients (27.0%) experienced a response to treatment and 84 patients (55.3%) reported a stable disease. Among them, the median duration of response was not estimable at the moment of the interim analysis. Disease control was achieved in 125 patients (82.2%).

A *post hoc* analysis of OS according to the ALBI grade showed that patients with ALBI grade 1 at baseline ($n = 77$) reported a better outcome (OS not estimable) compared with patients with ALBI grade 2 (median OS 15.2 months; 95% CI 10.7-17.3 months; $P < 0.001$). An exploratory analysis of efficacy in the BCLC B population is reported in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.104110.

DISCUSSION

AMETHISTA is the first prospective study investigating the safety and effectiveness of atezolizumab plus bevacizumab in a Western (Italian) population of patients with unresectable HCC, reporting consistent results with the IMbrave150 trial. Thus our findings further confirm previous data in a full Western population of patients, representing the first prospective study specifically dedicated to collecting safety information in a homogeneous population.[13,21]

At the cut-off date, the median observation time was 13.4 months [interquartile range 8.3-15.5 months; mean (SD) 12.1 (5.1) months], similar to the observation time reported in the data update from the IMbrave150 trial (15.6 months).[21] Safety results showed that the incidence of grade 3-5 bleeding/hemorrhages (11.4%) was globally comparable with the IMbrave150 trial; however, strict comparisons should be considered with caution due to some differences in the observation times (8.9 and 15.6 months for the IMbrave150 trial; Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.

Table 5. Overall incidence of TEAEs leading to discontinuation or interruption of any study treatment component

TEAEs	Overall, *n* (%)	Discontinuation of atezolizumab, *n* (%)	Discontinuation of bevacizumab, *n* (%)	Discontinuation of both, *n* (%)
TEAEs leading to permanent discontinuation of any study treatment	44 (29.5)	32 (21.5)	42 (28.2)	30 (20.1)
TEAEs leading to temporary interruptions of any study treatment	94 (63.1)	76 (51.0)	83 (55.7)	57 (38.3)

TEAEs, treatment-emergent adverse events.
n= number of patients.

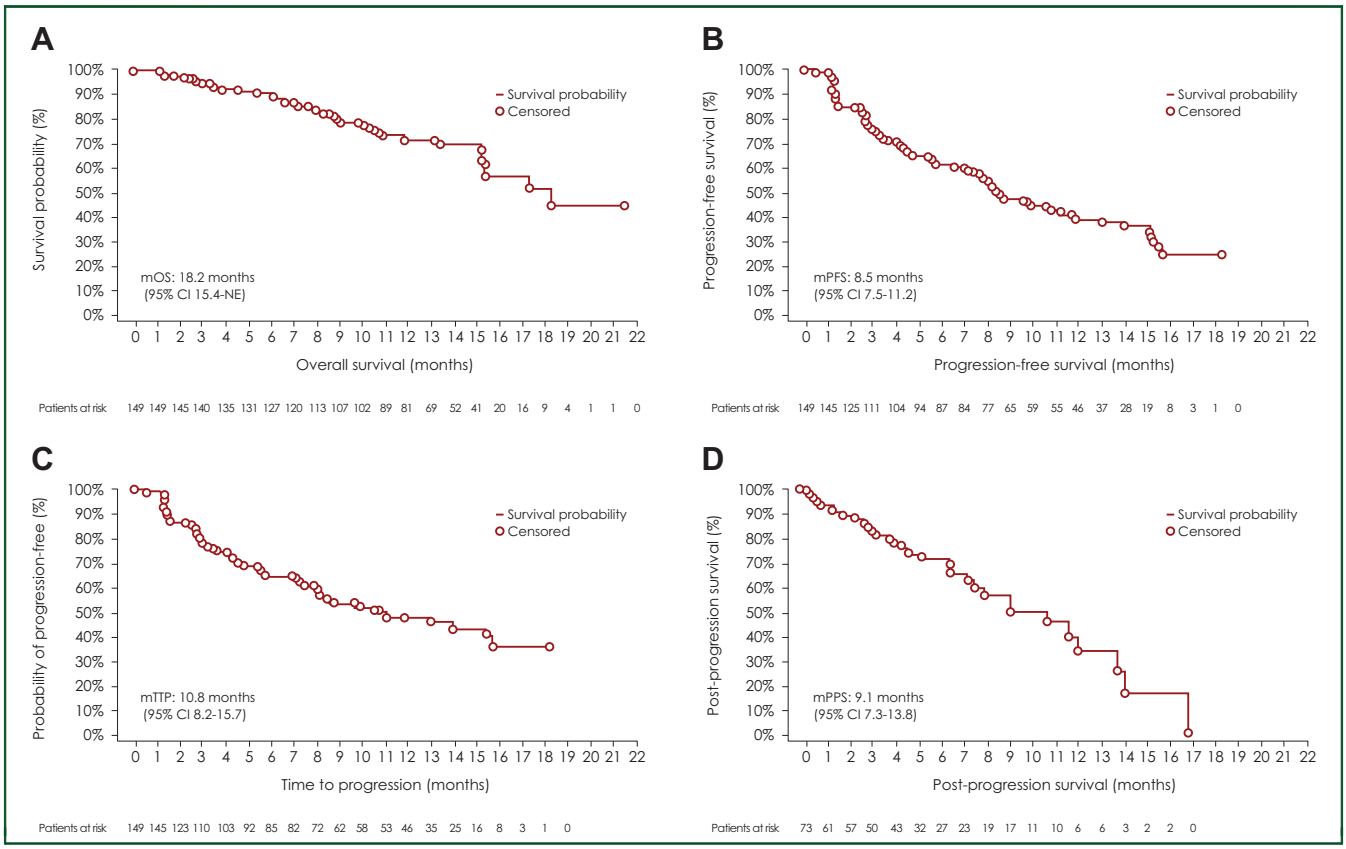

Figure 1. Kaplan–Meier analyses of overall survival (OS), progression-free survival (PFS), time to progression (TTP), and post-progression survival (PPS) for patients in the intention-to-treat population. (A) Kaplan–Meier estimate of OS; (B) Kaplan–Meier estimate of PFS; (C) Kaplan–Meier estimate of TTP; (D) Kaplan–Meier estimate of PPS.
m, median.

104110) and in patient baseline characteristics.[13,21] Few fatal bleeding cases were reported at similar rates to previous studies. Thus it is suggested to assess the bleeding risk from portal hypertension-related events (EGD) to provide for the optimal management of the patient,[27] even if this might not be enough to prevent severe bleeding events. Considering that the incidence of severe bleeding events was limited and in line with the previous findings, no specific features predicting the risk of severe bleeding could be identified from this study. This may also be related to the fact that such events were reported in only a few patients, making any statistical analysis unreliable. We support, however, the strategy of achieving the most effective variceal bleeding prophylaxis by either band ligation or beta-blockade before starting the combined atezolizumab plus bevacizumab treatment. Moreover, we would underline the importance of active monitoring and management of esophageal varices during the treatment.

Results of the other safety endpoints were consistent with the known safety profile of atezolizumab plus bevacizumab and the underlying disease; no new safety observations of interest have been identified up to the interim cut-off date. Notably, AEs leading to discontinuation of any or both atezolizumab and bevacizumab were higher in this study compared with the IMbrave150 study (29.5% for any AEs versus 22% in IMbrave150; 20.1% for both versus 10%). While it may partially relate to the sample size, conducting studies in geographically more homogeneous populations could help uncover predisposing conditions specific to certain populations. Given the speculative nature of this observation, this point warrants further investigations in future studies. For instance, preliminary safety data from the interim analyses of the phase IIIb study ATHECA, investigating the safety of atezolizumab plus bevacizumab in patients with unresectable HCC from 26 Spanish centers, align with this observation.[28] It is worth outlining that considering the long follow-up time, we could expect that the safety profile of atezolizumab and bevacizumab may be maintained over time.

The median OS was 18.2 months (95% CI 15.4 months to not evaluable). This result aligns with the updated data from the IMbrave150 trial (19.2 months; 95% CI 17.0-23.7 months) after a median of 15.6 months (range 0-28.6 months) of follow-up.[21] Compared with IMbrave150, the median PFS was slightly longer (8.5 months; 95% CI 7.5-11.2 months versus 6.8 months; 95% CI 5.7-8.3 months).[13,21] The response rate was also comparable (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.104110), even if a greater proportion of patients achieved stable disease, with ∼10% experiencing PD as their best response, compared with ∼20% in IMbrave150.[21] Some differences in baseline characteristics could have influenced the observed treatment outcomes, as the low incidence of extrahepatic disease can be associated with a less aggressive tumor phenotype and a

more favorable response to therapy. At the same time, this outcome was observed in a population of patients with liver-confined disease who had exhausted all available locoregional treatment options. However, this remains a speculative observation that deserves further investigation.

In addition, we found that patients with baseline ALBI grade 1 reported a better outcome in terms of OS compared with patients with ALBI grade 2 ($P < 0.001$). This aligns with findings from the IMbrave150 trial regarding the greater benefit in OS among patients with ALBI grade 1.[13]

In addition to clinical trials, real-world studies are available in the literature exploring the safety and efficacy of atezolizumab plus bevacizumab treatment for unresectable HCC,[29] in particular in elderly patients[30] and in patients with Child—Pugh class A or B liver cirrhosis.[31,32] Results of these studies suggest that atezolizumab plus bevacizumab treatment can be used efficaciously and safely despite age in patients with unresectable HCC and that a better hepatic function, such as modified albumin-bilirubin grade 1 or 2a, is thought to indicate a better condition for obtaining the best outcome with atezolizumab plus bevacizumab.[29-33]

Given the phase IIIb nature of the study, the results obtained are of great interest as they very strongly corroborate the findings about safety, and efficacy already reported and further confirm previous data in a full Western (Italian) population of patients. Moreover, these data were obtained from patients enrolled in a large number of Italian centers in a short time, therefore, in a context similar to the clinical practice. However, there are several limitations to consider, including the absence of a centralized review of responses and progressions, a lack of detailed information on MVI extension—particularly concerning patients with main portal vein thrombosis (VP4)—the absence of correlative science analyses on tumor tissues, and, as noted, differences in patient composition. These differences include liver disease etiology, the rate of underlying cirrhosis, and tumor extent compared with the IMbrave150 study, which should be interpreted with caution. Lastly, as the classification of the etiology of a patient's HCC was not a main focus at the time of study design, available data do not appear detailed enough to identify patients with metabolic dysfunction-associated steatotic liver disease, although this would be a topic of interest. At the same time, our paper presents the results of an interim analysis to promptly share the first results of the AMETHISTA trial. Further secondary and exploratory endpoints will be addressed in future final analyses, such as the fine assessment of survival data or assessment of how a diverse range of HCC etiologies may relate to the study findings and impact clinical management between Eastern and Western populations.

Given the complexity of the disease, the expertise of different specialists is required to provide optimal care. Consequently, the role of a multidisciplinary team and expert multidisciplinary tumor board should be emphasized and always considered in the management of patients with HCC, especially considering that real-world HCC management increasingly relies on factors independent of oncological staging.[34-37]

Conclusion

This interim analysis shows the safety and effectiveness of first-line atezolizumab plus bevacizumab in an Italian population of patients with unresectable HCC treated according to the AMETHISTA trial. These results are consistent with data from the IMbrave150 trial and further confirm this combination as a standard of care for systemic treatment-naive advanced and unresectable HCC.

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DISCLOSURE

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DATA SHARING

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of this writing, the request platform is Vivli (https://vivli.org/ourmember/roche/). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

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