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Original Research

Reproducible safety and efficacy of atezolizumab plus bevacizumab for HCC in clinical practice: Results of the AB-real study

Claudia Angela Maria Fulgenzi [a,b,1], Jaekyung Cheon [c,1], Antonio D'Alessio [a,d], Naoshi Nishida [e], Celina Ang [f], Thomas U. Marron [f], Linda Wu [f], Anwaar Saeed [g], Brooke Wietharn [g], Antonella Cammarota [d,h], Tiziana Pressiani [h], Nicola Personeni [d,h], Matthias Pinter [i], Bernhard Scheiner [i], Lorenz Balcar [i], Andrea Napolitano [j], Yi-Hsiang Huang [k,l], Samuel Phen [m], Abdul Rafeh Naqash [n], Caterina Vivaldi [o,p], Francesca Salani [o,p,q], Gianluca Masi [o,p], Dominik Bettinger [r], Arndt Vogel [s], Martin Schönlein [t], Johann von Felden [u], Kornelius Schulze [u], Henning Wege [u], Peter R. Galle [v], Masatoshi Kudo [e], Lorenza Rimassa [d,h], Amit G. Singal [m], Rohini Sharma [a], Alessio Cortellini [a], Vincent E. Gaillard [w], Hong Jae Chon [c,**], David James Pinato [a,x,*]

[a] *Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, Du Cane Road, W120HS London, UK*
[b] *Division of Medical Oncology, Policlinico Universitario Campus Bio-Medico, Rome, Italy*
[c] *Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea*
[d] *Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve Emanuele, Milan, Italy*
[e] *Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan*
[f] *Department of Medicine, Division of Hematology/Oncology, Tisch Cancer Institute, Mount Sinai Hospital, New York, NY, USA*
[g] *Department of Medicine, Division of Medical Oncology, Kansas University Cancer Center, Kansas City, KS, USA*
[h] *Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy*
[i] *Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria*
[j] *The Royal Marsden NHS Foundation Trust, 203 Fulham Road, SW36JJ London, UK*
[k] *Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[l] *Institute of Clinical Medicine, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan*

* *Corresponding author*: Medical Oncology, Imperial College London, Hammersmith Campus, Du Cane Road, W12 0HS, London, UK.
** *Corresponding author*: Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Republic of Korea. Fax: +82 31 780 3929.
E-mail address: minidoctor@cha.ac.kr (H.J. Chon), david.pinato@imperial.ac.uk (D.J. Pinato).
[1] These authors contributed equally and are to be considered co-authors.

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[m] Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA
[n] Medical Oncology/TSET Phase 1 Program, Stephenson Cancer Center, University of Oklahoma, Oklahoma City, USA
[o] Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[p] Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
[q] Sant'Anna School of Advanced Studies, Pisa, Italy
[r] Department of Medicine II (Gastroenterology, Hepatology, Endocrinology and Infectious Diseases), Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[s] Hannover Medical School, Hannover, Germany
[t] Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[u] Department of Gastroenterology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[v] University Medical Center Mainz, I. Dept. of Internal Medicine, Mainz, Germany
[w] Product Development Medical Affairs, F. Hoffmann-La Roche Ltd., Basel, Switzerland
[x] Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

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Abstract ***Background:*** IMbrave150 has established the superiority of atezolizumab plus bevacizumab over sorafenib in patients with unresectable hepatocellular carcinoma (HCC).
Methods: We generated a prospectively maintained database including patients treated with atezolizumab plus bevacizumab for unresectable HCC across Europe, Asia and USA. Clinico-pathologic characteristics were assessed for their prognostic influence on overall survival (OS) and progression-free survival (PFS) in univariable and multivariate analyses. Overall response rate by RECIST v1.1 and treatment-related adverse events (TRAEs) per CTCAE v.5.0 were reported.
Results: Out of 433 patients, 296 Child-Pugh A and ECOG performance status01 patients received atezolizumab plus bevacizumab in first line and were included. Patients were mostly male (82.7%), cirrhotic (75%) with history of viral hepatitis (65.9%). Overall, 68.9% had Barcelona Clinic Liver Cancer C-stage HCC with portal vein tumour thrombosis (PVTT, 35%) and extrahepatic spread (EHS, 51.7%). After a median follow-up of 10.0 months (95% confidence interval (CI): 9.4–10.4), median OS and PFS were 15.7 (95% CI: 14.5-NE) and 6.9 months (95% CI: 6.1–8.3), respectively. In the response-evaluable patients (n = 273), overall response rate was 30.8%. Overall, 221 patients (74.6%) developed TRAEs, with 70 (23.6%) reporting grade 3 or higher TRAEs; 25 (8.4%) patients had bleeding events. OS was independently associated with baseline Albumin-bilirubin (ALBI) grade and PVTT. Shorter PFS was associated with AFP$\geq$ 400 ng/ml, worse ALBI and presence of EHS.
Conclusion: This global observational study confirms the reproducible safety and efficacy of atezolizumab plus bevacizumab in routine clinical practice. Within Child-Pugh-A criteria, the presence of PVTT and higher ALBI grade identify patients with poorer survival.

1. Introduction

In 2019, after a decade characterised by limited therapeutic advancements, the IMbrave150 phase III study established the anti-PD-L1 monoclonal antibody atezolizumab in combination with the anti-Vascular endothelial growth factor (VEGF) bevacizumab as the new standard of care for unresectable hepatocellular carcinoma (HCC) [1]. For the first time since the approval of sorafenib, the experimental arm demonstrated both prolonged overall survival (OS) and progression-free survival (PFS) compared to sorafenib, and, at the same time, to improve objective response rate (ORR) and quality of life [2,3]. The survival advantage of atezolizumab plus bevacizumab was preserved across all subgroups, with the exception of those with non-viral aetiology, leading to an unprecedented median OS of 19.2 months [2]. The positive results of the IMbrave150 study led international guidelines to recommend the combination as the standard first-line regimen for those patients mirroring the inclusion criteria of the study [4].

Little high-quality evidence exists to suggest whether the adoption of atezolizumab and bevacizumab in routine practice is characterised by similar effectiveness

and safety compared to the original clinical trial population [5,6]. A precise description of clinical outcomes among within-indication patients receiving atezolizumab plus bevacizumab is currently lacking. This is of major consequence in HCC, where new standards of care compete with sequential utilisation of tyrosine kinase inhibitors: a strategy that has been recognised to extend median OS to 19 months following the judicious use of systemic therapy [7]. In addition, evidence of the differentiated outcomes of combination immunotherapy in patients with viral versus non-viral aetiology of liver disease is lacking in routine practice [8].

In this study, we present the results of an international collaborative effort aimed at portraying clinical outcomes of patients treated with atezolizumab and bevacizumab according to label.

2. Methods

We generated a prospectively maintained database including patients receiving atezolizumab plus bevacizumab for unresectable HCC in 14 tertiary care centres across Europe, USA and Asia. Inclusion criteria and methods are reported in Supplementary. The clinical outcomes for this population have been reported in the context of previous publications [6].

Ethical approval was granted by the Imperial College Tissue Bank (Reference Number R16008) and by local institutional review boards at each participating institution.

3. Results

3.1. Patients

At the time of data cut-off, on the 1st April 2022, 433 patients were included in the dataset. The entirety of patients had received atezolizumab 1200 mg every 3 weeks plus bevacizumab 15 mg/kg every 3 weeks intravenously until disease progression, loss of clinical benefit or unacceptable toxicity from January 2019 to January 2022 as in routine clinical practice. Dose modifications or interruptions of either drug followed the summary of products characteristics. After removing patients not meeting the inclusion criteria (Fig. 1), 296 patients were retained for analyses.

Baseline clinico-pathologic characteristics of our cohort are summarised in Table 1. In brief, most patients were male (82.7%) and had liver cirrhosis (75%). Overall, 65.9% of patients had HCC secondary to Hepatitis B (40.6%) or Hepatitis C virus infection (25.3%). Aetiology of chronic liver disease for the remaining patients included alcohol-associated liver disease (14.9%), non-alcoholic steatohepatitis (11.5%) and cryptogenic aetiology (7.7%). The median age was 66 years (IQR: 59–73). All patients had preserved liver function. ECOG PS was 0 (47%) or 1 (53%). Overall, the majority of patients had Barcelona Clinic Liver Cancer stage C HCC (68.9%), and 34.5% of patients had baseline Alpha-feto protein (AFP) ≥400 ng/ml. In total, 73.7% of patients had received prior loco-regional treatments (LRTs).

3.2. Overall survival

After a median follow-up of 10.0 months (95% confidence interval (CI): 9.40–10.40), 128 patients (43.2%) were still receiving treatment at the time of database lock, 154 patients had discontinued due to progression and 94 patients had died. Median treatment duration was 7.3 months (95% CI: 6.30–8.70). Median OS was 15.7 months (95% CI: 14.50-NE) (Fig. 2a). After testing for the proportionality of hazards (global

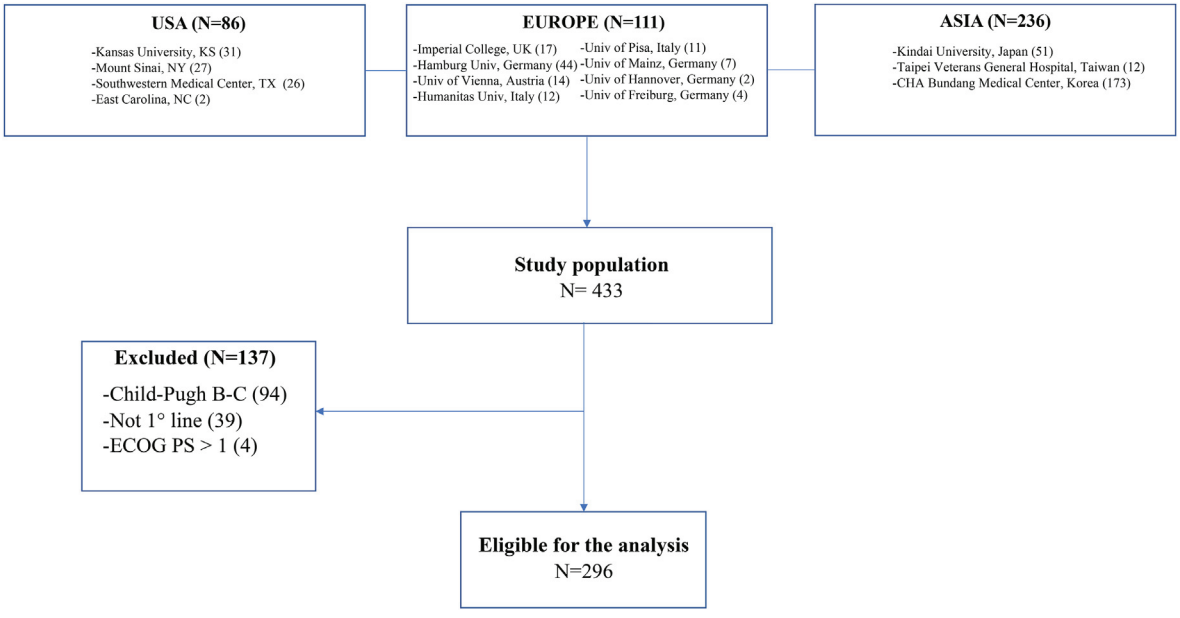

Fig. 1. Study flow chart.

Table 1
Description of baseline characteristics in the whole cohort.

Variable	N (%)
Age	
>65 y	158 (53.3%)
≤65 y	138 (46.7%)
Gender	
Male	245 (82.7%)
Female	51 (17.3%)
ECOG PS	
0	139 (47.0%)
1	157 (53.0%)
BCLC	
B	92 (31.1%)
C	204 (68.9%)
EHS	
Present	169 (51.7%)
Absent	127 (48.3%)
AFP	
≥400 ng/ml	102 (34.5%)
<400 ng/ml	194 (65.5%)
Child-Pugh	
5	190 (64.2%)
6	106 (35.8%)
ALBI	
1	161 (54.4%)
2	133 (44.9%)
3	2 (0.7%)
Cirrhosis	
Present	222 (75.0%)
Absent	74 (25.0%)
Etiology	
Viral	195 (75.9%)
Non-viral	101 (24.1%)
HBV	120 (40.6%)
HCV	75 (25.3%)
PVTT	
Present	104 (35.0%)
Absent	192 (65.0%)
Previous surgery	
Yes	83 (28.0%)
No	213 (72.0%)
Previous RFA	
Yes	46 (15.5%)
No	250 (84.5%)
Previous TACE	
Yes	122 (41.2%)
No	174 (58.8%)
Previous LRT	
0–1	78 (26.3%)
2	151 (51.0%)
≥ 3	67 (22.7%)

p = 0.44), we performed proportional-hazards Cox regression analysis to assess the prognostic role of baseline characteristics. As reported in Table 2, AFP ≥400 ng/ml (p = 0.009), Child-Pugh score (CPS) (6 versus 5, p < 0.001), presence of portal vein tumour thrombosis (PVTT) (p < 0.001), ALBI grade (2 versus 1, p < 0.001) and receipt of prior LRT (yes versus no, p < 0.001) were prognostic factors for OS in the univariate analysis. ALBI (p < 0.001) and presence of PVTT (p = 0.03) were confirmed to be independent prognostic factors for OS in the multivariate model shown in Supplementary Fig. 1. Supplementary Fig. 2A and 2B depict the difference in OS between patients with ALBI grade 1 (mOS: NE; 95% CI: 16.85-NE months) and 2 (mOS: 10.03; 95% CI: 8.58–12.34), and in those with PVTT (mOS: 10.03; 95% CI: 8.88-NE) and without (mOS:17.03; 95% CI: 14.96-NE), respectively.

Patient-level survival from the published IMbrave150 OS Kaplan–Meier curves were reconstructed as reported in methods section [2]. When comparing estimates from IMbrave150 with those reported in our study, univariate Cox regression model showed no difference in OS estimates across clinical trial versus real-life cohorts (hazard ratio (HR): 0.86; 95% CI: 0.66–1.12; p = 0.30, Fig. 3a).

3.3. PFS

At the time of data cut-off, 174 patients had experienced progression or death. Median PFS was 6.9 months (95% CI: 6.10–8.30, Fig. 1b). Among all the tested variables (Table 2), AFP (≥400 ng/ml versus < 400 mg/ml, p = 0.009) and ALBI grade (p = 0.003) were prognostic factors for PFS in the univariate and multivariate (p = 0.030; p = 0.010) analyses; the presence of EHS was also an independent prognostic factor for PFS in the multivariate model (p = 0.020, Table 2). Supplementary Fig. 3–C depict Kaplan–Meier curves for PFS stratified according to AFP concentration, ALBI grade and presence of EHS. After extracting patient-level PFS data from IMbrave150 and comparing estimates with our cohort, we found that median PFS of patients treated within the trial did not differ from those receiving the combination in real life (mPFS: 6.91 months; 95% CI: 5.70–8.60 versus 6.91; 95% CI: 6.10–8.30; HR:0.90; 95% CI: 0.74–1.10; p = 0.3, Fig. 3b).

3.4. Objective response

At the time of data cut-off, 273 patients were evaluable for radiologic response; the remaining 23 patients had not had the first radiological reassessment at the time of data cut-off. According to RECIST v1.1, 30.8% achieved an objective response, with 8 patients (2.9%) experiencing complete radiologic response and 76 (27.8%) patients experiencing a partial response. A total of 128 (46.9%) patients achieved stable disease, resulting in a disease control rate of 77.7%. Primary disease progression occurred in 61 patients (22.3%). Median time to best response was 1.6 months (IQR: 1.32–2.76), and median duration of response was 12.4 months (95% CI: 7.63–17.17). As reported in Supplementary Table 1, receipt of prior LRT (p = 0.002) was associated with a higher ORR (35.8% versus 15.9%). We then compared OS of patients achieving radiological response to that of those reporting stable disease or progression as best response. To account for immortal-time bias, we

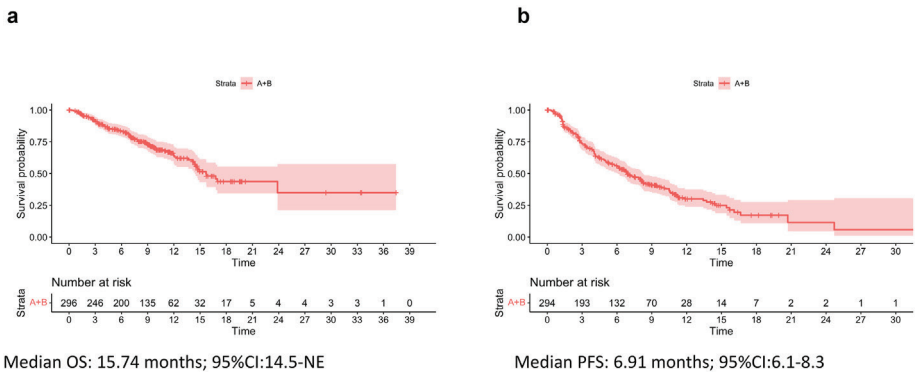

Fig. 2. Kaplan–Meier curves for overall survival (OS) (a) and progression-free survival (PFS) (b) in the whole cohort.

performed a landmark analysis at 2, 4 and 6 months. As showed in Fig. 4a–c, patients reporting radiological response had significantly longer overall survival at each landmark timepoint (HR: 0.10; 95% CI: 0.04–0.21).

3.5. Safety

Overall, 221 patients (74.7%) developed at least one treatment-related adverse event (TRAE) as per investigator assessment, with 70 subjects (23.6%) reporting grade 3 or 4 TRAEs (66 grade 3 and 4 grade 4, respectively). Atezolizumab-related AEs of any grade occurred in 63 patients (21.3%). Overall, 25 (8.4%) patients had bleeding events (9 of grade 3 and 2 grade 4), with oesophageal varices being the most common site of bleeding (5.1%).

As reported in Supplementary Table 3, the most common TRAEs of any grade were proteinuria (30.4%) and hypertension (28.3%); hepatotoxicity and proteinuria were the most common grade 3 AEs (5%). Overall, 25 patients (8.4%) permanently discontinued the combination due to TRAEs.

As reported in Supplementary Table 2, patient without liver cirrhosis and with ECOG PS 1 had higher incidence of grade 3 or higher TRAEs; none of the baseline factors was found to be associated with hepatotoxicity, and the presence of PVTT, ALBI grade and CPS were associated with higher incidence of bleeding events. Out of the 15 patients experiencing variceal bleeding, data about oesophago-gastro-duodenoscopy (EGD) before treatment initiation was available for 12: among them, 10 had endoscopy <6 months before

Table 2
Univariate and multivariate analyses for overall survival and progression-free survival.

	Overall survival HR; 95% CI (p-value)		Progression-free survival HR; 95% CI (p-value)	
	Univariate	Multivariate	Univariate	Multivariate
Age >65 versus ≤ 65	1.14; 0.75–1.61 (0.50)		0.94; 0.70–1.27 (0.70)	
Gender M versus F	0.89; 0.53–1.51 (0.70)		0.79; 0.53–1.16 (0.20)	
BCLC C versus B	1.42; 0.90–2.23 (0.10)		1.29; 0.94–1.79 (0.10)	
AFP ≥400 versus < 400	1.72; 1.15–2.59 (0.009)	1.46; 0.68–2.23 (0.08)	1.51; 1.11–2.05 (0.009)	1.44; 1.04–1.98 (0.03)
ALBI 2 + 3 versus 1	3.65; 2.36–5.64 (<0.001)	2.64; 1.63–4.31 (<0.001)	1.57; 1.16–2.2 (0.003)	1.49; 1.08–2.04 (0.01)
Child-Pugh 6 versus 5	2.42; 1.61–3.64 (<0.001)	1.47; 0.94–2.29 (0.09)	1.271; 0.93–1.74 (0.10)	
Cirrhosis Y versus N	1.21; 0.74–1.99 (0.40)		0.97; 0.68–1.37 (0.80)	
PVTT Y versus N	2.03; 1.39–2.99 (<0.001)	1.58; 1.03–2.41 (0.03)	1.25; 0.93–1.68 (0.10)	
EHP spread Y versus N	0.93; 0.62–1.40 (0.70)		1.31; 0.97–1.77 (0.08)	1.42; 1.05–1.94 (0.02)
ECOG PS 1 versus 0	1.26; 0.83–1.90 (0.30)		1.13; 0.84–1.53 (0.40)	
Aetiology viral versus non-viral	0.95; 0.62–1.5 (0.80)		1.23; 0.89–1.70 (0.20)	
Previous LRT Y versus N	0.48; 0.31–0.72 (<0.001)	0.77; 0.49–1.22 (0.27)	0.74; 0.53–1.04 (0.09)	0.87; 0.60–1.25 (0.44)

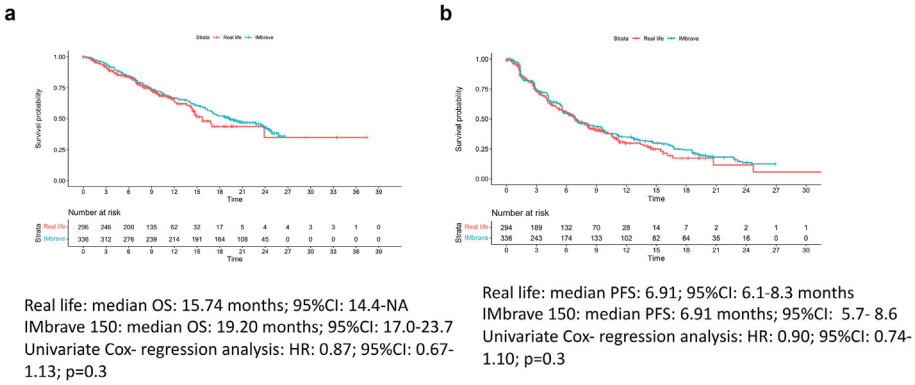

Fig. 3. Kaplan–Meier curves for OS (a) and PFS (b) in the IMbrave150 study and in the real-life cohort. OS, overall survival; PFS, progression-free survival.

treatment initiation and 2 had EGD more than 6 months before treatment start. Among these patients, one had prior grade 3 varices, six had grade 2 and three reported grade 1 oesophageal varices. The remaining 2 patients had no evidence of varices at baseline. Varices was treated according to local guidelines prior to treatment start.

4. Discussion

The systemic treatment of HCC has consistently represented a challenge for clinicians and patients [9]. Along with intrinsic chemoresistance and with the immune-suppressive nature of the liver immune microenvironment, progressive HCC competes with underlying chronic liver disease in determining patients' prognosis and suitability to treatment [10]. Combination immunotherapy has reshaped the landscape of advanced HCC by affording unprecedented response and survival compared to patients treated with tyrosine kinase inhibitors [1,11]. There is, however, limited data to suggest whether the positive results of atezolizumab and bevacizumab reported in the IMbrave150 study have translated into clinical benefit outside clinical trials. Eligibility to combination immunotherapy is not universal in patients with advanced HCC and combined PD-L1/VEGF blockade is not devoid of significant adverse events: cardiovascular toxicity, bleeding risk and immune-pathology secondary to checkpoint inhibition can be life-threatening and patient selection is key to optimise treatment outcomes [12]. Attention for so called 'real-world evidence' studies has progressively widened over the years [13] and well-conducted, post-registration observational studies have become essential to reproduce and confirm efficacy and safety data reported in clinical trials [14,15]. AB-Real is to our knowledge the largest and most geographically diverse study documenting outcomes from atezolizumab plus bevacizumab therapy in a large cohort of advanced HCC treated in 14 centres across 3 continents. By analysing a population that mirrors the reference clinical trial cohort, we demonstrate that effectiveness and safety profiles of atezolizumab plus bevacizumab in clinical practice are comparable to those reported in the dedicated phase III study. After a median follow-up of approximately 10 months, with an ORR of 30.8% and a

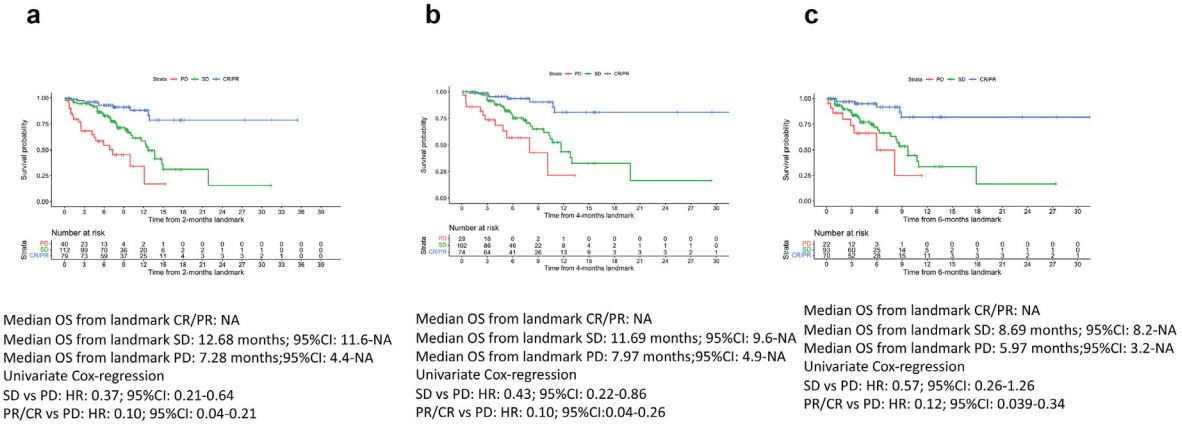

Fig. 4. Kaplan–Meier curves for OS according to radiological response with landmark at 2 (a), 4 months (b) and 6 months (c). OS, overall survival; PFS, progression-free survival.

disease control rate of 77.7%, our study demonstrates the measures of anti-tumour efficacy that are comparable with those reported in the IMbrave150 study.

In addition, the computerised reconstruction of patient-level data from IMbrave150 trial allowed us to draw a direct comparison of survival across trial versus real-world cohorts, further corroborating the reproducibility of the OS and PFS estimates reported in the updated results of the study [2].

An important objective of our study is to define the prognostic factors associated with outcome from atezolizumab and bevacizumab therapy in unresectable/advanced HCC. An important finding from our study is the recognition that patients who achieve a radiologically appreciable response are the ones achieving longer survival, contributing to establish the surrogate value of ORR as an early measure of long-term survival benefit in these patients. Whilst median OS was not reached in responders, patients achieving SD had almost doubled OS compared to primary progressors. This is in keeping with data from the IMbrave 150 trial [16].

In addition to radiologic response, baseline ALBI grade and the presence of PVTT were independently associated with OS in our study. A worse ALBI grade, along with AFP concentration >400 ng/ml at baseline and the presence of EHS were independently predictive of worse PFS. These clinico-pathologic traits are recognised prognostic factors for HCC, having been reproducibly shown to impact survival outcomes across various therapeutic modalities [17,18]. The prognostic role of ALBI grade [19], a validated score across various therapeutic modalities for HCC [20], including immunotherapy [21], is of particular importance in our study as it confirms the independent role of liver function in determining the outcome of patients with HCC, even when stringent criteria of CP-A class are applied [22].

A recently published translational study has highlighted how PD-1 monotherapy might result in the expansion of CD8+/PD-1+ immune exhausted T-cell in animal models of NASH-HCC, leading to the concern that patients with non-viral HCC may be less capable of mounting efficient immune-reconstitution following checkpoint inhibition [23]. In our cohort, 75.9% of patients had evidence of virally induced HCC, an estimate close to the 70% figure reported within the IMbrave150 [24]. However, differently from the IMbrave150, when categorised according to aetiology, patients with non-viral HCC had comparable outcomes compared with those with virally induced HCC, suggesting the preserved efficacy of combination immunotherapy across aetiologies of chronic liver disease. It should be highlighted that the prevalence of viral aetiology in our cohort, and the absence of specific stratification in the IMbrave150, might have impaired the reliability of the subgroup analysis. As pre-clinical and translational research continues to expand to understand therapeutic vulnerabilities associated with NASH-HCC, clinical data in support of reduce immune-responsiveness of non-viral HCC have been generated in patients with advanced disease almost exclusively treated with anti-PD-1/PD-L1 monotherapy and were not confirmed by the HIMALAYA trial, wherein the survival benefit of dual checkpoint inhibition was preserved even in non viral patients [25]. Our findings may suggest concurrent VEGF inhibition to abrogate the potentially detrimental role of NASH in pre-conditioning the quality and activity of T-cell following treatment with PD-1/PD-L1 monotherapy and highlight the need to further investigate actionable drivers of anti-cancer immunity that are specifically enriched in NASH-HCC.

Aside from considerations relating to efficacy, which had already been described in previous studies by our group [6], this study provides an exhaustive description of TRAEs stemming from atezolizumab and bevacizumab exposure, confirming the safety profile of both drugs. Despite being characterised by a lower incidence of all-grade TRAEs compared to IMbrave150 as a likely result of a less rigorous record of TRAEs in routine clinical practice, our study reports that the proportion and the frequency of TRAEs are comparable with clinical trial data. Proportion of permanent discontinuations of both drugs, occurring in 8.4% of patients in our series and 7% in the phase III study, was also reproducible across trial versus real-world data. One of the most clinically significant risks from atezolizumab and bevacizumab is bevacizumab-induced bleeding events. Overall, the incidence of gastrointestinal bleeding was consistent with previous reports, and no grade 5 haemorrhagic event occurred in our study. Among patients who developed variceal bleeding, data about pre-treatment endoscopy were available for 12 out of 15, and most of them reported evidence of varices at the time of endoscopy, which were treated per local guidelines. According to available information, 2 of the patients reporting variceal bleeding had endoscopy outside the 6-month timeframe reported in the inclusion criteria of the IMbrave150, a finding that stresses the importance of adequate and timely screening of oesophageal varices prior to bevacizumab exposure. In our cohort, haemorrhagic events were unsurprisingly almost three times (5.7% versus 13.5%) more frequent in patients who had evidence of neoplastic portal thrombosis: PVTT is in fact known to cause increased portal pressure which ultimately facilitates variceal development [26]. Furthermore, despite evidence of preserved liver function in all patients, we describe a two-fold increase in the incidence of haemorrhagic events to >10% in patients with CPS 6 or ALBI ≥2, compared to approximately 5% in those with CPS 5 or ALBI 1. Whilst descriptive and requiring validation in prospective studies, these findings are provocative in highlighting liver function and radiologically appreciable measures of portal hypertension as measures to estimate the risk of potentially life-threatening AEs.

Several limitations should be considered when appraising our data. Every retrospective study is limited by incomplete data collection and lack of standardisation in prior eligibility assessment. Examples of missingness in our dataset are pre-treatment endoscopy dates in 36% of patients and incomplete reconstruction of extent of PVTT. Particular attention should be made when interpreting data about prior EGD in our cohort: the large percentage of missing data is mainly related to incomplete data reporting and not to the absence of screening which is a strong recommendation in clinical practice. Lack of independent review limits the quality of radiology assessment and the absence of more granular data regarding patients' comorbidities does not allow for a complete reconstruction of confounders. Furthermore, some of data included in our analyses overlap with previous studies published by our group, partially reducing the originality of the findings [6]. Despite these limitations, our study is characterised by the largest geographic diversity in patients' provenance to date in documenting outcomes from atezolizumab and bevacizumab. The cohort size of this study and the length of follow-up compares favourably to that of other phase II/III studies in this field—factors that are undeniably contributory to the consistency observed between the results of our study and those of landmark clinical trials in unresectable HCC.

In conclusion, AB-Real is the first global retrospective study to demonstrate the reproducibility and wider generalisability of outcomes of atezolizumab and bevacizumab in advanced/unresectable HCC. PVTT and ALBI grade were identified as independent prognostic factors for OS and were associated with an increased risk of hemorrhagic events in a population characterised by well-preserved liver functional reserve. AB-Real describes the role of ORR as a surrogate for OS benefit in patients treated with atezolizumab plus bevacizumab. As combination immunotherapy continues to expand in daily clinical practice, the early evaluation of response may help clinicians to identify patients deriving protracted benefit from systemic therapy.

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Authors contribution

All the authors contributed to data generation, writing and revising the original draft. Claudia A.M. Fulgenzi contributed to data curation, formal analysis, conceptualisation, and visualisation; Andrea Napolitano contributed to formal analysis; David J. Pinato was responsible for supervision and project administration.

Raw data will be made available upon request to the authors.

Conflict of interest statement

AD received educational support for congress attendance from Roche. JvF received advisory board fees from Roche. HW received lecture fees and advisory board honoraria from Roche, Bayer, Ipsen, Eisai, BMS. VEG is employee and shareholder of F. Hoffmann-La Roche, Ltd. AS received research grants (to institution) from AstraZeneca, Merck, Bristol Myers Squibb, Exelixis, Clovis, KAHR medical, Actuate therapeutics, Incyte Corp. and Advisory board fees from AstraZeneca, Bristol Myers Squibb, Merck, Exelixis, and Pfizer. PRG reports a consulting or advisory role and received honoraria from AdaptImmune, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Lilly, Merck Sharp & Dohme, Roche, and Sirtex; has been on a speakers bureau for straZeneca, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Lilly, Merck Sharp & Dohme, Roche, and Sirtex; has received research funding from Bayer and Roche; has provided expert testimony for Lilly; and has received travel or accommodation expenses from AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Lilly, and Roche. DB has received lecture and speaker fees from Bayer Healthcare, the Falk Foundation Germany and consulting fees from Boston Scientific. AV reports honoraria for speaker, consultancy and advisory role from Roche, AstraZeneca, EISAI, Bayer, Merck, Bristol Myers Squibb, Merck Sharp & Dohme, Incyte, PierreFabre, Ipsen, and Sanofi. BS received travel support from Gilead, Ipsen and AbbVie. NP received consulting fees from Amgen, Merck Serono, Servier; lectures fees from AbbVie, Gilead, Lilly, Sanofi; travel expenses from Amgen, ArQule; and institutional research funding from Basilea, Merck Serono, Servier. TP received consulting fees from Bayer; and institutional research funding from Bayer, Lilly, Roche. RS received consulting fees for EISAI, Roche, Bayer, SIR-TEX, Novartis; research funding (to institution) from Incyte, Novartis, Astex Pharmaceuticals, Bayer and Boston Scientific. MP is an investigator for Bayer, BMS,

Ipsen, Lilly, and Roche; he received speaker honoraria fromBayer, BMS, Eisai, Lilly, MSD, and Roche; he is a consultant for Bayer, BMS, Eisai, Ipsen, Lilly, MSD, and Roche; he received travel support from Bayer and BMS. AC received con-sulting fees from MSD, BMS, AstraZeneca, Roche; speakers' fee from AstraZeneca, MSD, Novartis and Astellas. LR received consulting fees from Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi, Servier, Taiho Oncology, Zymeworks; lecture fees from AbbVie, Amgen, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, Roche, Sanofi; travel expenses from Ipsen; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks. AGS has served on advisory boards or as consultant for Genentech, AstraZeneca, Eisai, Bayer, Exelixis, BMS, Roche, Glycotest, Exact Sciences, FujiFilm Medical Sciences, GRAIL. DJP received lecture fees from ViiV Healthcare, Bayer Healthcare, BMS, Roche, Eisai, Falk Foundation, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, DaVolterra, Mursla, Exact Sciences and Astra Zeneca; research funding (to institution) from MSD and BMS. VEG is employed by F. Hoffmann-La Roche Ltd., Basel, Switzerland. All remaining authors have declared no conflicts of interest. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilised in the production of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.08.024.

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