Atezolizumab plus bevacizumab versus lenvatinib for unresectable hepatocellular carcinoma: a large real-life worldwide population

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Abstract *Background and aims:* Atezolizumab plus bevacizumab and lenvatinib have not been compared in a randomised controlled trial. We conducted a retrospective multi-centre study to compare the clinical efficacy and safety of lenvatinib and atezolizumab with bevacizumab as a first-line treatment for patients with unresectable HCC in the real-world scenario.
Methods: Clinical features of lenvatinib and atezolizumab plus bevacizumab patients were balanced through inverse probability of treatment weighting (IPTW) methodology, which weights patients' characteristics and measured outcomes of each patient in both treatment arms. Overall survival (OS) was the primary end-point.
Results: The analysis included 1341 patients who received lenvatinib, and 864 patients who received atezolizumab plus bevacizumab. After IPTW adjustment, atezolizumab plus bevacizumab did not show a survival advantage over lenvatinib HR 0.97 (p Z 0.739). OS was prolonged by atezolizumab plus bevacizumab over lenvatinib in viral patients (HR: 0.76; p Z 0.024). Conversely, OS was prolonged by lenvatinib in patients with non-alcoholic steatohepatitis/non-alcoholic fatty liver disease (HR: 1.88; p Z 0.014).

In the IPTW-adjusted population, atezolizumab plus bevacizumab provided better safety profile for most of the recorded adverse events.
Conclusion: Our study did not identify any meaningful difference in OS between atezolizumab plus bevacizumab and lenvatinib. Although some hints are provided suggesting that patients with non-alcoholic steatohepatitis/non-alcoholic fatty liver disease might benefit more from lenvatinib therapy and patients with viral aetiology more from atezolizumab plus bevacizumab.

1. Introduction

Sorafenib has been the only anticancer drug proven to improve overall survival (OS) in patients with unresectable hepatocellular carcinoma (HCC) in the last 15 years [1,2]. Subsequently, lenvatinib was approved as a first-line treatment option after the results of the REFLECT trial. In that study, lenvatinib had a non-inferior OS compared to sorafenib (median 13.6 versus 12.3 months, respectively), but significant improved progression-free survival (PFS), time to progression (TTP) and objective response rate (ORR) were demonstrated [3].

In several cancer settings, immunotherapy emerged as a promising therapeutic option, but randomised clinical trials failed to demonstrate a survival benefit from immunotherapy as single agent in advanced HCC patients [4,5], until recently. Indeed, the combination of the anti-programmed death ligand 1 (anti-PD-L1) atezolizumab plus the anti-vascular endothelial growth factor (anti-VEGF) bevacizumab showed to considerably improve OS, PFS, ORR and quality life compared to sorafenib in the IMbrave150 trial [6]. In particular, patients treated with atezolizumab plus bevacizumab had a median OS of 19.2 months compared to 13.4 months in patients receiving sorafenib (hazard ratio [HR] 0.66, p Z 0.0009). The advantages of immunotherapy in these patient population were highlighted by numerous other immunotherapy trials [7,8].

However, no randomised controlled trial has been conducted to compare atezolizumab plus bevacizumab to lenvatinib. According to a recent network meta-analysis based on the updated results of the IMbrave150 trial, the survival benefit of atezolizumab plus bevacizumab is not statistically significant when compared to lenvatinib (HR 0.63 for OS and HR 0.91 for PFS) [9]. OS on atezolizumab with bevacizumab was found to be superior compared to lenvatinib (log-rank: 0.001) with a HR of 0.59 in our matching-adjusted indirect comparison analysis between IMbrave150 data and real-world lenvatinib data [10].

In the real-world setting, Beom Kyung Kim *et al.* recently showed that the comparison between the two treatments did not result in any differences in ORR (32.6% versus 31.5%; p Z 0.868), OS (19.9 months in the lenvatinib arm versus not reached in the atezolizumab plus bevacizumab arm; p Z 0.897), PFS (7.3 months in the lenvatinib arm versus 5.7 months in the

atezolizumab plus bevacizumab arm, p = 0.391), or incidence of adverse events (AEs) (any grade $p = 0.282$; Grade ≥ 3 $p = 0.141$) [11].

In order to gain a better understanding of the effects in terms of OS, we used real-world data to create balanced cohorts of patients receiving either atezolizumab plus bevacizumab or lenvatinib and compared clinical outcomes between the two weighted populations.

2. Methods

Patients treated with atezolizumab plus bevacizumab or lenvatinib as first-line therapy for advanced-stage HCC (BCLC-C) or intermediate HCC (BCLC-B) who were deemed ineligible for first- or re-treatment with surgical or locoregional therapies were included in the study population. Between May 2015 and April 2022, the overall cohort included Western and Eastern populations from 42 centres in five countries (Italy, Germany, Portugal, Japan and the Republic of Korea), with data for analysis collected retrospectively. Patients who were eligible had their HCC diagnoses confirmed histologically or clinically according to international guidelines, and none had previously received systemic therapy. The use of either treatment followed the same inclusion criteria as the registration trials. The current study was approved by the ethics committees at each centre, and it followed the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws, as well as the European Parliament and Council Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data, which was enacted on April 27, 2016.

2.1. Treatments and definitions

All patients were treated with lenvatinib, until atezolizumab plus bevacizumab approval. After atezolizumab plus bevacizumab approval, the choice between the two therapies was left to physician in-charge with discretion. Lenvatinib was administered as described in the REFLECT trial (12 mg if baseline bodyweight was $\geq$60 kg or 8 mg if baseline body weight was <60 kg, given once daily orally) [3]. Atezolizumab plus bevacizumab was administered as described in the IMbrave150 trial (1200 mg of atezolizumab plus 15 mg per kilogramme of body weight of bevacizumab intravenously every 3 weeks) [6].

Treatment interruptions and dose reductions were allowed to manage AEs as local practice. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Patients were followed every 2–3 months with multiphasic scanning technique. Tumour assessment was carried out regardless of dose interruption until radiological disease progression or imaging had become clinically irrelevant. When progression was diagnosed, the adoption of any subsequent anticancer medication depended on the local physician decision.

The Clinical Practice Guidelines of the European Associations for the Study of the Liver, the Study of Diabetes and the Study of Obesity were utilised to define the non-alcoholic steatohepatitis/non-alcoholic fatty liver disease (NASH/NALFD) population and NAFLD-related HCC [12].

2.2. Statistical analysis

Categorical variables were reported as the number of cases and percentage, continuous variables were expressed as median and interquartile range (IQR). OS was computed as the interval between the date of therapy start until the date of death for any reason. TTP was computed as the interval between the date of therapy start until the date on which tumour progression was recorded. Median follow-up time was calculated with the reverse Kaplan–Meier method.

Differences in baseline characteristics between groups were estimated with the Fisher exact test or Kruskal–Wallis test. Differences were also estimated using standardised differences (d-value), which allowed to estimate the eventual imbalance between treatment groups regardless of their size: differences were negligible when d-values <0.1, values between 0.1 and 0.3 indicate small differences, values between 0.3 and 0.5 indicate moderate differences and values > 0.5 indicate large differences. A propensity score (PS) was calculated, representing the likelihood to receive atezolizumab plus bevacizumab conditional to covariates. All clinical and tumour variables available when treatment started were used for PS calculation to avoid incurring into the possible imbalance of other parameters not correlated with the probability of receiving atezolizumab plus bevacizumab but with unknown effect on the outcome. The obtained PS was then used to generate stabilised inverse probability of treatment weights (IPTW) through appropriate math, which were used to weight each clinical feature, as well as measured outcomes, of each patient in both groups. After weighting baseline characteristics, d-values were recalculated, and adequate balance was declared if all variables returned $d < 0.1$.

Once the weighted pseudo-population of patients was obtained, differences between outcomes of atezolizumab plus bevacizumab and lenvatinib were analysed. IPTW-adjusted Kaplan–Meier curves were calculated to graphically compare survivals among groups. For survival analyses, interactions between therapy and grouping variables of interest were explored through standard or IPTW-weighted log-rank [PMID: 26514380] and Cox regressions. All regressions were performed using the number of involved centres as strata to provide robust variance estimation. Results were expressed as HR or odds ratios (OR). When assessing OS in the

Table 1
Baseline characteristics of the study population before and after IPTW adjustment.

Variables	Before IPTW adjustment				After IPTW adjustment		
	Atezolizumab þ bevacizumab (n Z 864)	Lenvatinib (n Z 1341)	p-value*	d value	Atezolizumab þ bevacizumab (n Z 864)	Lenvatinib (n Z 1343)	d value
Clinical							
Age (years)	72 (65, 79)	72 (65, 79)	0.377	0.044	72 (64, 78)	72 (65, 79)	0.015
Male	690 (79.9%)	1054 (78.6%)	0.486	0.031	682 (79.0%)	1058 (78.8%)	0.005
Asian	791 (91.6%)	1181 (88.1%)	0.011	0.115	768 (88.9%)	1197 (89.2%)	0.010
Hepatitis C	270 (31.3%)	501 (37.4%)	0.003	0.129	299 (34.6%)	470 (34.9%)	0.007
Hepatitis B	203 (23.5%)	278 (20.7%)	0.126	0.067	184 (21.3%)	288 (21.5%)	0.006
Viral (HCV or HBV)	474 (54.9%)	779 (68.1%)	0.146	0.065	484 (56.0%)	758 (56.5%)	0.010
NAFLD/NASH	59 (6.8%)	251 (18.7%)	0.001	0.362	126 (14.6%)	190 (14.1%)	0.015
Previous surgery	307 (35.5%)	349 (26.0%)	0.001	0.207	269 (31.2%)	405 (30.1%)	0.023
Previous ablation	195 (22.6%9	332 (24.8%)	0.260	0.051	210 (24.2%)	321 (23.9%)	0.008
Previous TACE	368 (42.6%)	783 (58.4%)	0.001	0.320	452 (52.3%)	698 (52.0%)	0.007
ChildePugh B	62 (7.2%)	153 (11.4%)	0.001	0.146	86 (10.0%)	132 (9.8%)	0.007
ALBI	—2.2 (—2.5, —1.9)	—2.3 (—2.6, —1.9)	0.968	0.031	—2.2 (—2.5, —1.9)	—2.2 (—2.6, —1.9)	0.011
ECOG PS1-2	222 (25.7%)	239 (17.8%)	0.001	0.192	185 (21.4%)	286 (21.3%)	0.002
Tumour							
Log10 AFP (ng/mL)	1.7 (0.8, 2.9)	1.6 (0.8, 2.9)	0.619	0.024	1.7 (0.9, 2.9)	1.7 (0.8, 2.9)	0.006
Vascular invasion	188 (20.3%)	272 (20.3%)	0.421	0.036	185 (21.5%)	285 (21.2%)	0.006
Extra-hepatic disease	314 (36.3%)	488 (36.4%)	1.000	0.001	316 (36.6%)	491 (36.6%)	0.002

Continuous data are reported as medians and IQR. Corresponding d-values were calculated after their logarithmic transformation to account for eventual non-parametric distributions.
d-values <0.1 indicate negligible differences, values between 0.1 and 0.3 indicate small differences, between 0.3 and 0.5 indicate moderate differences and >0.5 indicate large differences.
* p-values derived from Fisher exact, chi-square, KruskaleWallis tests or log-rank test in the unweighted population.

IPTW-adjusted subgroups, the impact of second-line therapies was handled through a time-dependent approach. No a-priori level of significance was set in the present analyses. The whole analysis was repeated for each subgroup considered. Analyses were performed using Stata (StataCorp. Stata Statistical Software: Release 15) and R-project (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Clinical characteristics

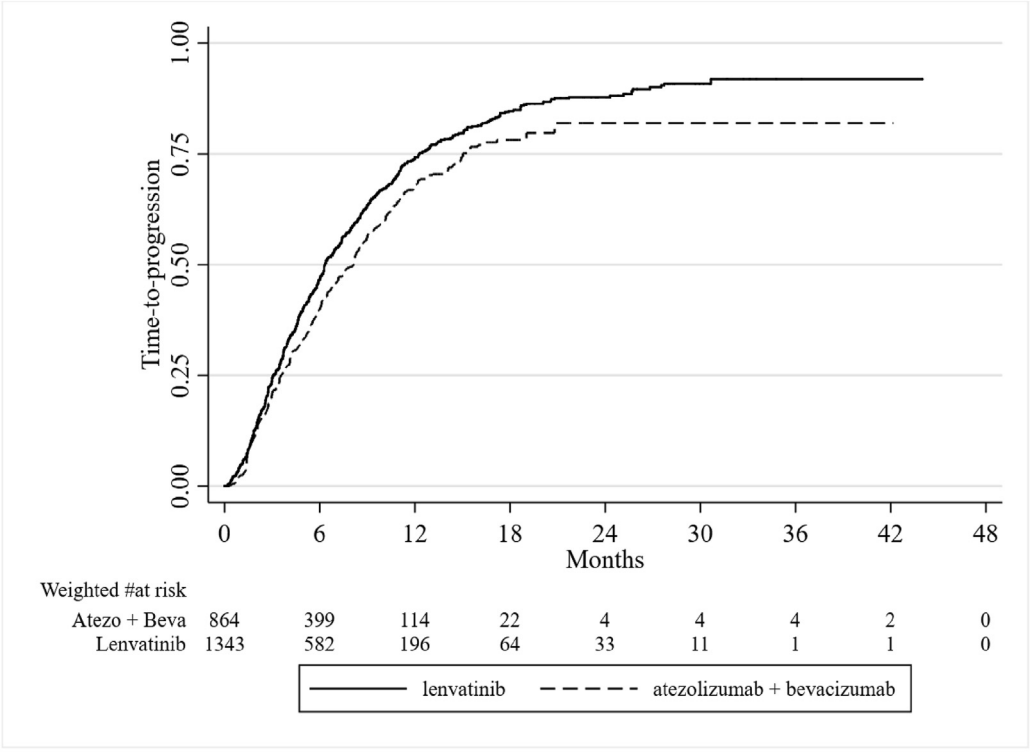
Data from a total of 2205 patients were analysed: 1341 received lenvatinib and 864 received atezolizumab plus bevacizumab. These two groups differed for several features (Table 1). Briefly, patients receiving atezolizumab plus bevacizumab were more frequently Asian compared to those receiving lenvatinib (p Z 0.011). Patients receiving lenvatinib were more frequently hepatitis C virus (HCV)-positive or had NASH/NAFLD (p Z 0.003 and 0.001, respectively). Lenvatinib patients most frequently had previous transarterial chemoembolization (TACE), whereas atezolizumab plus bevacizumab patients most frequently had prior surgery (p Z 0.001, both). A larger proportion of patients classified as ECOG-PS1-2 was present in the atezolizumab plus bevacizumab group, whereas a larger proportion of ChildePugh B patients was present in the lenvatinib group (p Z 0.001, both).

3.2. Primary outcomes

Compared to patients receiving atezolizumab plus bevacizumab, follow-up of patients treated with lenvatinib was longer (Supplementary Table 1), so that these latter showed a higher proportion of tumour progression events and deaths (p Z 0.001, both). In this unadjusted population, the median TTP of patients receiving atezolizumab plus bevacizumab was 8.1 months (IQR: 3.5, 15.5) and that of patients receiving lenvatinib was 6.3 months (IQR: 3.2, 12.3), resulting in a log-rank test Z 0.001. After handling for variance due to centres' effect, the HR was 0.81 (95%CI: 0.64, 1.02) in favour of atezolizumab plus bevacizumab (p Z 0.073). The median OS of patients receiving atezolizumab plus bevacizumab was 16.4 months (IQR: 8.8, not reached) and that of patients receiving lenvatinib was 16.1 months (IQR: 8.6, 44.0), resulting in a log-rank test Z 0.346. After adjustment for centres' effect and second-line therapies received, the HR was 0.94 (95%CI: 0.79, 1.12; p Z 0.440) in favour of atezolizumab plus bevacizumab.

3.3. Inverse proportion of treatment weight adjustment

After IPTW-adjustment, baseline clinical and tumour characteristics were similar between the two groups (Table 1), as indicated by a d-value <0.10 in all cases. In this population, the median TTP (Fig. 1, panel A) was 8.2 months (IQR: 3.6, 15.0) with atezolizumab plus bevacizumab and 6.3 months (IQR: 3.1, 12.3) with



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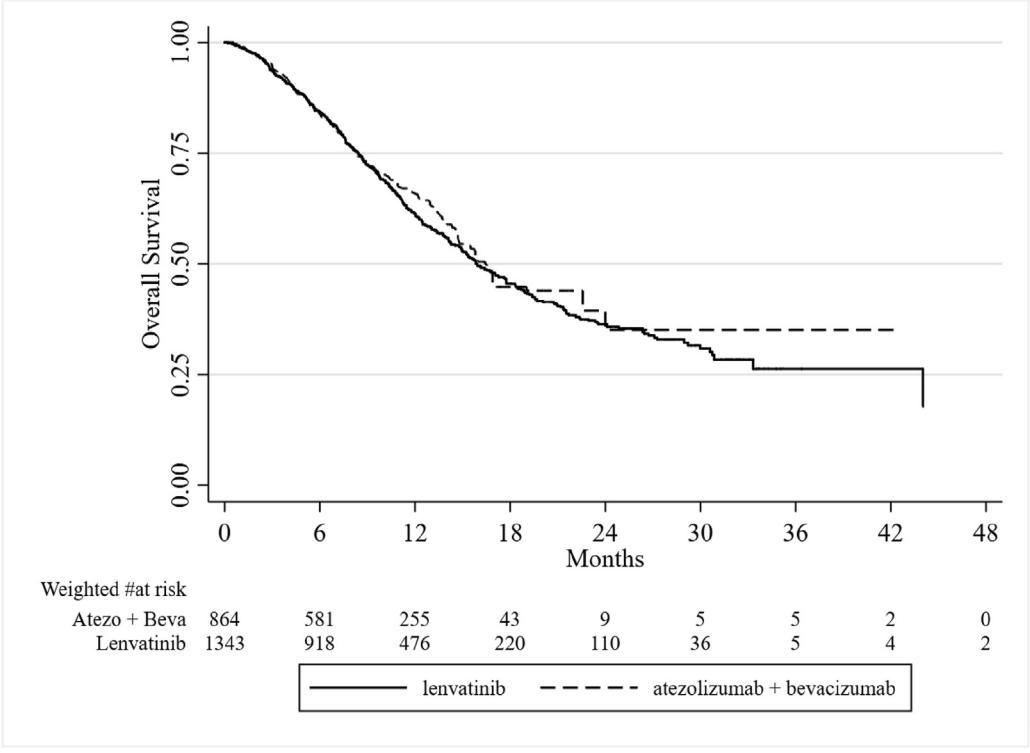

B

Fig. 1. Time to progression (TTP; Panel A) and overall survival (OS) in the IPTW-adjusted population (Panel B). The IPTW-log-rank test for TTP was 0.001; however, when variance due to the centres' effect was introduced through the Cox model, the HR was 0.82 (95%CI: 0.64, 1.06; p Z 0.117). The IPTW-log-rank test for OS was 0.445. When variance due to the centres' effect was introduced through the Cox model, the HR was 0.97 (95%CI: 0.80, 1.17; p Z 0.739).

lenvatinib, resulting in an adjusted log-rank test Z 0.001. After handling for variance due to the centres' effect, the final HR was 0.82 (95%CI: 0.64, 1.06; p Z 0.117).

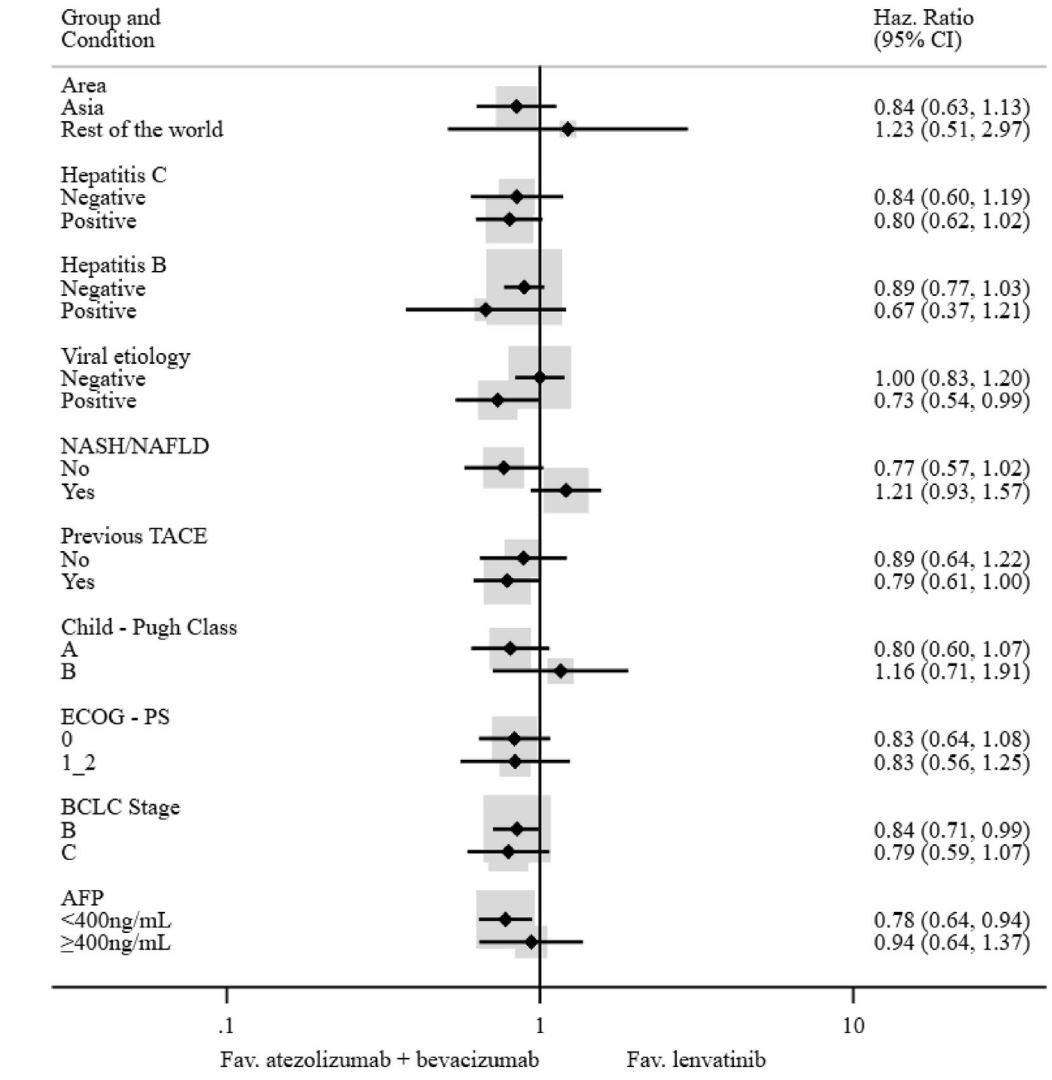

Fig. 2. Forest-plot reporting the effect of atezolizumab plus bevacizumab versus lenvatinib on time to progression in the IPTW-adjusted population.

The median OS (Fig. 1, panel B) with atezolizumab plus bevacizumab was 16.4 months (IQR: 8.2, not reached) and 15.8 months (IQR: 8.4, 44.0) with lenvatinib. The adjusted log-rank test was Z 0.445. After adjustment for centres' effect and second-line therapies received, this difference resulted in a HR for atezolizumab plus bevacizumab of 0.97 (95%CI: 0.80, 1.17; p Z 0.739).

3.4. Primary outcomes in subgroups

In the IPTW-adjusted population, atezolizumab plus bevacizumab prolonged TTP compared to lenvatinib (Fig. 2) in viral patients (HR: 0.73; 95%CI: 0.54, 0.99; p Z 0.048), in BCLC-B patients (HR: 0.85; 95%CI: 0.71, 0.99; p Z 0.049) and in patients with AFP<400 ng/mL (HR: 0.78; 95%CI: 0.64, 0.94; p Z 0.014). When analysing OS (Fig. 3 and Supplementary Fig. 1), a survival benefit for atezolizumab plus bevacizumab over lenvatinib was observed in viral patients (HR: 0.76; 95% CI: 0.61, 0.96; p Z 0.024). Conversely, OS was prolonged by lenvatinib in patients with NASH/NAFLD (HR: 1.88; 95%CI: 1.16, 3.01; p Z 0.014) (Fig. 3 and Supplementary Fig. 2).

3.5. Safety

In the IPTW-adjusted population, atezolizumab plus bevacizumab provided a better safety profile for most of the recorded AEs (Table 2). Despite immune-related toxicities affected only these patients (any grade 14.4%, grade 3e4 3.2%), atezolizumab plus

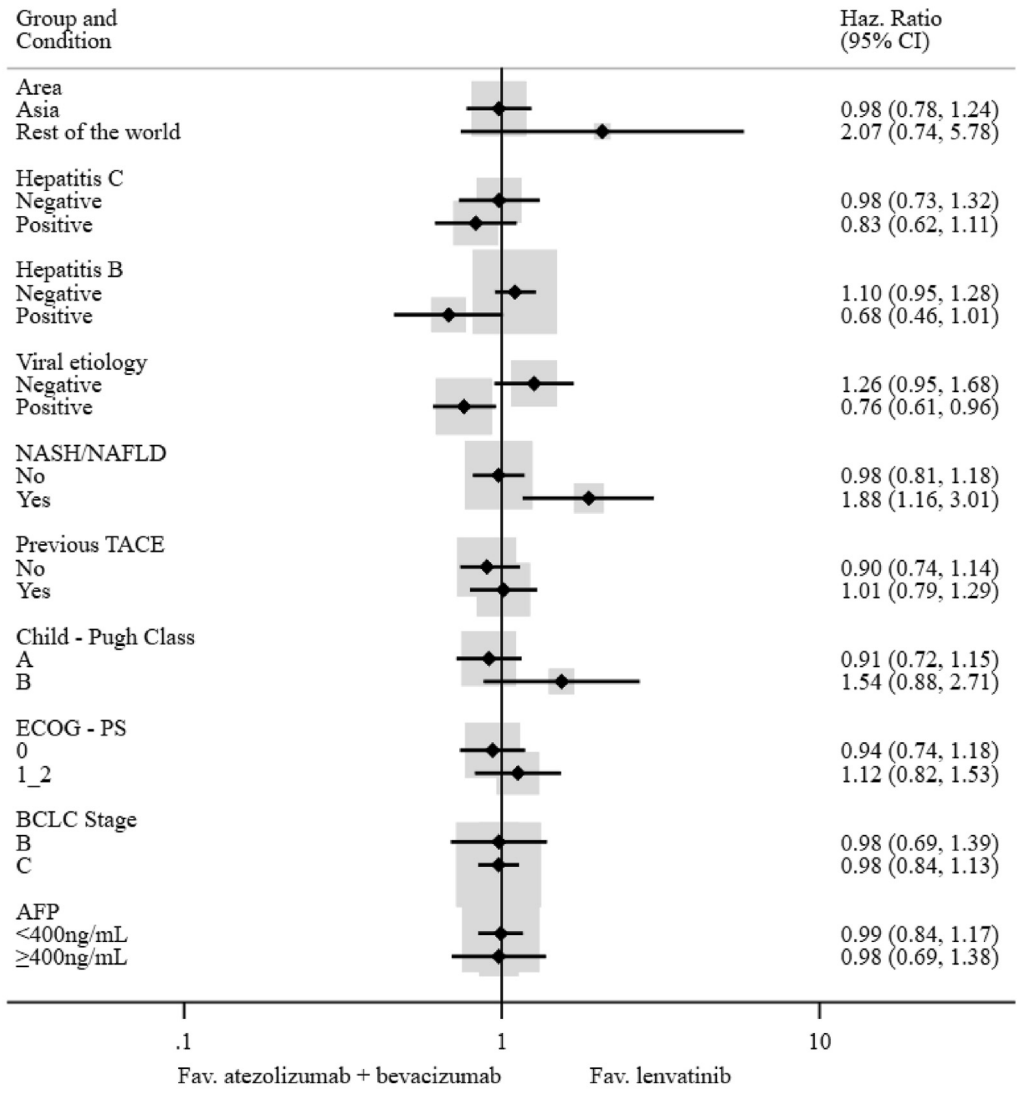

Fig. 3. Forest-plot reporting the effect of atezolizumab plus bevacizumab versus lenvatinib on overall survival in the IPTW-adjusted population, adjusted for second-line therapies received.

bevacizumab was consistently associated to a decrease of any AEs (OR: 0.41; 95%CI: 0.22, 0.77; p Z 0.009) and of those graded as 3e4 (OR: 0.43; 95%CI: 0.26, 0.75; p Z 0.005). Anorexia was reduced (OR: 0.53; 95% CI: 0.31, 0.88; p Z 0.019), in particular when graded as 3e4 (OR: 0.32; 95%CI: 0.13, 0.80; p Z 0.018). This also applied to diarrhoea of any grade (OR: 0.37; 95%CI: 0.22, 0.62; p Z 0.001) and when graded as 3e4 (OR: 0.33; 95%CI: 0.13, 0.85; p Z 0.025). Grade 3e4 fatigue was also reduced by atezolizumab plus bevacizumab (OR: 0.39; 95%CI: 0.17, 0.84; p Z 0.021). Finally, handefootеskin reaction (OR: 0.10; 95%CI: 0.04, 0.17; p Z 0.001) and hypothyroidism of any grade (OR: 0.16; 95%CI: 0.08, 0.34; p Z 0.001) were also less frequent compared to lenvatinib.

4. Discussion

In the present study, we observed, in a large cohort of 2205 patients, that after adequate adjustment, atezolizumab plus bevacizumab provided an HR of 0.97 (95% CI: 0.80, 1.17; p Z 0.739) for OS compared to lenvatinib, suggesting that there were no differences in terms of survival benefit between the two cohorts of patients. The present results may appear somehow unexpected if compared to the available data derived from randomised clinical trials. Indeed, the REFLECT trial [3] showed no difference in terms of OS between lenvatinib and sorafenib, whereas atezolizumab plus bevacizumab provided longer OS compared to sorafenib in the IMbrave150 trial [6].

Table 2
Safety outcomes in the two treatment arms in the IPTW-adjusted population.

Variables	Atezolizumab þ bevacizumab (n Z 864)	Lenvatinib (n Z 1343)	Odds ratio (95%CI)	p-value*
Any adverse event	603 (69.8%)	1140 (84.9%)	0.41 (0.22, 0.77)	0.009
G3-G4	421 (48.8%)	921 (68.7%)	0.43 (0.26, 0.75)	0.005
Hypertension	223 (25.8%)	422 (31.5%)	0.76 (0.35, 1.64)	0.453
G3-G4	57 (6.6%)	80 (6.0%)	1.11 (0.61, 2.03)	0.724
Fatigue	214 (24.8%)	431 (32.1%)	0.69 (0.36, 1.33)	0.252
G3-G4	16 (1.9%)	62 (4.7%)	0.39 (0.17, 0.84)	0.021
Anorexia	171 (19.8%)	427 (31.8%)	0.53 (0.31, 0.88)	0.019
G3-G4	16 (1.8%)	73 (5.4%)	0.32 (0.13, 0.80)	0.018
Diarrhea	76 (8.8%)	278 (20.7%)	0.37 (0.22, 0.62)	0.001
G3-G4	6 (0.7%)	29 (2.2%)	0.33 (0.13, 0.85)	0.025
HFS reaction	21 (2.5%)	300 (22.3%)	0.10 (0.04, 0.17)	0.001
G3-G4	5 (0.6%)	29 (2.2%)	0.27 (0.06, 1.16)	0.075
Hypothyroidism	52 (6.0%)	379 (28.2%)	0.16 (0.08, 0.34)	0.001
G3-G4	3 (0.4%)	13 (0.9%)	0.42 (0.09, 1.87)	0.233
Proteinuria	239 (27.6%)	327 (24.4%)	1.18 (0.57, 2.46)	0.631
G3-G4	53 (6.1%)	96 (7.1%)	0.84 (0.39, 1.83)	0.640

* p-values derived from logistic regression.

Atezolizumab þ bevacizumab determined immune toxicities of any grade in 14.4% of patients and G3-G4 toxicity in 3.2%.

In order to interpret these data, there are a few points that should be considered. To begin with, the primary end-point in the REFLECT trial was OS non-inferiority testing: this goal was achieved, but concurrently a trend towards superiority of lenvatinib over sorafenib was also apparent [3]. Additionally, the secondary end-points, such as PFS, TTP, and ORR, showed that lenvatinib was superior to sorafenib. Furthermore, several previous real-world studies have shown that lenvatinib performs better in clinical practice than in randomised clinical trials [13e22], which could be attributed to improved AE management expertise. Previous evidence suggested that more experience with sorafenib management was linked to better survival outcomes [23,24]. Since sorafenib and lenvatinib belong to the same drug class and share several pharmacological characteristics, it is plausible that prior experience with sorafenib resulted in a shorter learning curve in the management of lenvatinib AEs by physicians, which could explain why real-world studies reported better clinical outcomes than randomised trials.

Indeed, in the few real-world experiences that are currently available atezolizumab plus bevacizumab showed worse survival outcomes than those seen in the registration study.

Atezolizumab plus bevacizumab is the first immunotherapy combination approved in the HCC setting, which means that even many physicians focussed on HCC are approaching this type of treatment for the first time. As a result, despite the good safety profile and better manageability of immunotherapy than TKIs, a certain time necessary to learn how to manage new treatments must be considered. Aside from randomised clinical trials, only a limited amount of information about the comparison of atezolizumab plus bevacizumab and lenvatinib is currently available, primarily from meta-analyses and a few real-world experiences.

Another important point to consider is the use of subsequent therapies after the first-line treatment adopted. Even though both cohorts had the same percentage of patients treated with second lines, differences in treatment types were noted. A significantly higher percentage of patients in the lenvatinib cohort received subsequent locoregional therapy compared to the atezolizumab plus bevacizumab group (18.1% versus 6.3%, respectively). Furthermore, only 6.8% of patients in the lenvatinib cohort received immunotherapy as a follow-up treatment, whereas 18.8% of patients in the atezolizumab plus bevacizumab arm received lenvatinib as a second-line treatment. Despite the differences in terms of subsequent therapy were considered as an adjustment factor in all the IPTW analyses and therefore their effects should have been mitigated, it is impossible to rule out that the influence on the final survival results was really null. Since several therapeutic options are currently available as second-line treatment for advanced HCC [25e27], more research about the best sequence of treatment after either lenvatinib or atezolizumab plus bevacizumab is highly warranted in the near future.

In addition to the previous issues, it must be considered that the real-life sample we considered in the analysis included a significant proportion of Child-ePugh class B patients, which instead were not represented in the registration trials of atezolizumab plus bevacizumab. Consequently, the higher proportion of ChildePugh B patients could have influenced the lower OS in the atezolizumab plus bevacizumab arm in our investigation.

Our analysis revealed a significant benefit in terms of OS in favour of lenvatinib in patients with NASH/NAFLD (HR of 0.50; p = 0.018) and significant benefit in term of TTP OS in favour of atezolizumab plus bevacizumab in patients with viral aetiology (HR: 0.73; p = 0.048; HR: 0.76; p = 0.024, respectively), in the IPTW-adjusted populations. This finding is in line with new evidence focussing on the role of aetiology in advanced HCC, in particular in patients' treatment with only anti-PDL1 or with anti-VEGF. Conversely, HIMALAYA trial highlighted the efficacy of an anti-PDL1 plus anti-CTLA4 in non-viral patients [7]. Indeed, it has been hypothesised that aetiology (viral versus non-viral) has a significant impact on HCC biology and host immune response, and that NASH/NAFLD HCC patients are less responsive to immunotherapy. Pfister and colleagues reported a correlation between an increased number of hepatic CD8 PD1 T cells induced by immunotherapy and an impairment of immune surveillance, thus triggering hepatocarcinogenesis in mouse model of NASH [26]. In the same work, by performing a meta-analysis on three phase 3 immunotherapy studies, the authors highlighted no survival benefit from immunotherapy in the subset of patients with non-viral aetiology; conversely, survival was improved in HBV and HCV patients [28]. It must be stressed that this meta-analysis was conducted using published data and includes non-homogeneous trials that were conducted using both single drugs and combinations, in first- and second-line settings. As a result, the findings can only be viewed as hypothesis-generating.

Based on these results, our research group recently performed a multicentre retrospective analysis on a large cohort of patients treated with lenvatinib as first-line treatment for advanced disease and showed that NASH-related aetiology is an independent positive prognostic and predictive factor for OS [29,30]. Conversely, in the recent real-word experience reported by Beom Kyung Kim and collaborators, no differences were reported in terms of OS between patients with viral or non-viral aetiology in patients treated with atezolizumab plus bevacizumab or lenvatinib. These contrasting results could be ascribed to a smaller sample size which could limit the power of the analysis and might not permit to highlight potential differences in terms of survival outcomes in patients treated with atezolizumab plus bevacizumab or lenvatinib. Nevertheless, patients with NASH-related HCC who were treated with lenvatinib had a higher ORR than those treated with atezolizumab plus bevacizumab (36% versus 10%, respectively). To date, no evidence exists on the role of aetiology in the clinical decision process for advanced HCC patients.

In patients with intermediate stage (HR: 0.85; p = 0.049) and in patients with AFP 400 ng/mL (HR: 0.78; p = 0.014), our study showed a substantial benefit in terms of TTP in favour of atezolizumab with bevacizumab. The point of intermediate stage, it is the same recommendation of the last BCLC system version that no longer recommends TACE as a reference treatment for all intermediate stages and proposes systemic treatment for diffuse or infiltrating B-stage HCC.

In terms of safety, atezolizumab plus bevacizumab was well tolerated associated to fewer adverse events than lenvatinib. In clinical practice, this is a particularly interesting aspect. Since patients treated with atezolizumab plus bevacizumab and those treated with lenvatinib have similar survival outcomes (except when only considering the NASH/NAFLD population), the safety profile becomes a critical factor to consider when deciding on the best therapeutic option for HCC patients.

The current study suffers from some limitations. To begin with, the lack of a standardised and stringent follow-up protocol makes the estimation of TTP unreliable. Second, even when using the IPTW analysis, a retrospective analysis of real-world data cannot provide the same level of evidence as randomised controlled trials. However, the applied statistical design allowed for a good balance between the two treatment arms and a significant reduction in potential confounders. Obviously, our analysis cannot account for unmeasured confounding, but this is a feature of randomised trials as well, so we believe that the current findings, even if they come from a retrospective study, can provide useful and reliable information. Another limitation of our study was that we didn't collect the duration of treatment and causes of treatment discontinuation; These data were important to understand the worse survival outcome in the real-world experiences of atezolizumab plus bevacizumab.

In conclusion, our study did not identify any meaningful overall difference in survival between atezolizumab plus bevacizumab and lenvatinib. Although some hints are provided suggesting that patients with NASH/NAFLD might benefit more from lenvatinib therapy and patients with viral aetiology might benefit more from atezolizumab plus bevacizumab, future large prospective trials are needed to better understand the potential role of aetiology in the clinical management of these patients.

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Authors' contributions

Conception and design: A. Casadei Gardini, Alessandro Cucchetti.

Acquisition of data (acquired and managed patients): All authors.

Analysis and interpretation of data: A. Casadei Gardini, Alessandro Cucchetti.

Writing, review, and/or revision of the manuscript: A. Casadei-Gardini, M. Rimini, Alessandro Cucchetti.

Final approval of manuscript: All authors.

Institutional review board statement

The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki.

Informed consent statement

Written informed consent for treatment was obtained for all patients.

Data availability statement

Data are available upon request from the authors.

Conflict of interest statement

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests.

L Rimassa has received consulting fees from Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, 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 AstraZeneca; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks. A.C.G. has received grants and personal fees from MSD, Eisai, Bayer, and is an advisor for MSD, Eisai, Bayer, Bristol-Myers Squibb, AstraZeneca and GSK.

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