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Original Research

Sequential therapies after atezolizumab plus bevacizumab or lenvatinib first-line treatments in hepatocellular carcinoma patients

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Hepatocellular carcinoma;
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Lenvatinib;
Sorafenib;
TACE

Abstract ***Introduction:*** The aim of this retrospective proof-of-concept study was to compare different second-line treatments for patients with hepatocellular carcinoma and progressive disease (PD) after first-line lenvatinib or atezolizumab plus bevacizumab.
Materials and methods: A total of 1381 patients had PD at first-line therapy. 917 patients received lenvatinib as first-line treatment, and 464 patients atezolizumab plus bevacizumab as first-line.
Results: 49.6% of PD patients received a second-line therapy without any statistical difference in overall survival (OS) between lenvatinib (20.6 months) and atezolizumab plus bevacizumab first-line (15.7 months; p = 0.12; hazard ratio [HR] = 0.80). After lenvatinib first-line, there wasn't any statistical difference between second-line therapy subgroups (p = 0.27; sorafenib HR: 1; immunotherapy HR: 0.69; other therapies HR: 0.85). Patients who underwent trans-arterial chemo-embolization (TACE) had a significative longer OS than patients who received sorafenib (24.7 versus 15.8 months, p < 0.01; HR = 0.64). After atezolizumab plus bevacizumab first-line, there was a statistical difference between second-line therapy subgroups (p < 0.01; sorafenib HR: 1; lenvatinib HR: 0.50; cabozantinib HR: 1.29; other therapies HR: 0.54). Patients who received lenvatinib (17.0 months) and those who underwent TACE (15.9 months) had a significative longer OS than patients treated with sorafenib (14.2 months; respectively, p = 0.01; HR = 0.45, and p < 0.05; HR = 0.46).
Conclusion: Approximately half of patients receiving first-line lenvatinib or atezolizumab plus bevacizumab access second-line treatment. Our data suggest that in patients progressed to atezolizumab plus bevacizumab, the systemic therapy able to achieve the longest survival is lenvatinib, while in patients progressed to lenvatinib, the systemic therapy able to achieve the longest survival is immunotherapy.

1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver tumour and represents an important global health challenge, being the fifth most frequent malignancy and the fourth cause of neoplastic death [1]. Fortunately, the therapeutic landscape of this neoplasm has greatly expanded in the last decade thanks to the approval of various therapeutic options both in the first and the second-line setting [2]. In the first-line setting, we have four treatments options available, the two tyrosine kinase inhibitors (TKI) sorafenib and lenvatinib, the combination of the anti-programmed cell death ligand 1 (PD-L1) atezolizumab with the anti-vascular endothelial growth factor (VEGF) bevacizumab, and the combination of a single primary dose of the anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) tremelimumab with the anti PD-L1 durvalumab [2].

With regards to later-lines setting, the RESORCE and the CELESTIAL trials led to the approval of two other TKIs, respectively regorafenib and cabozantinib [3,4]. Notably, regorafenib was approved in the second-line setting in patients who tolerated first-line sorafenib therapy [3]. The inclusion criteria of the CELESTIAL trials instead allowed for the use of cabozantinib in both second and third-line patients who have progressed to first-line sorafenib [4]. An anti-VEGF receptor (R) 2, ramucirumab, is also available in second-line setting thanks to the demonstrated superiority over placebo in the REACH-2 trial in patients with baseline α-fetoprotein levels greater than 400 ng/ml in patients who progressed to sorafenib [5]. The Food and Drug Administration (FDA) has also approved the use of immunotherapeutic drugs, the anti PD-1 pembrolizumab and the combination of the anti-CTLA4 ipilimumab with the anti PD-1 nivolumab, in second-line setting after sorafenib based on the two phase II trials, respectively, KEYNOTE-224 and CheckMate 040 [6,7].

All of these studies were conducted in patients who progressed to first-line with sorafenib and had placebo as the control arm, as current first-line and second-line treatment options were not yet available. However, the most frequently used first-line treatments nowadays are lenvatinib and atezolizumab plus bevacizumab, as the combination of durvalumab and tremelimumab is not yet reimbursed in many countries. Upon progression after these two first-line treatments, the standard of care in many countries is sorafenib, due to the lack of reimbursement for other therapeutic sequences. Moreover, no randomised phase III studies have yet been conducted to compare the different available second-line drugs for HCC patients progressed to first-line lenvatinib or atezolizumab plus bevacizumab [2]. This retrospective multicenter study was designed to provide this comparison for the first time in a large real-world population.

2. Materials and methods

2.1. Study population

The study population derived from a retrospective analysis of prospectively collected patients progressed to

atezolizumab plus bevacizumab or lenvatinib as first-line treatment for advanced HCC (Barcelona clinic liver cancer [BCLC] C) or intermediate HCC (BCLC-B) [8].

The overall cohort included Western and Eastern patient populations from 46 centres in 5 countries (Italy, Germany, Portugal, Japan, and the Republic of Korea) treated with first-line treatment with lenvatinib between July 2010 and February 2022, and with atezolizumab plus bevacizumab between May 2018 and May 2022. Eligible patients had HCC diagnosis histologically confirmed or clinically confirmed according to international guidelines.

The end-point of this proof-of-concept study was to compare the overall survival (OS) achieved by different second-line therapies.

The choice between therapies was left to the treating physician both in the first-line and second-line setting. Lenvatinib was administered as described in the REFLECT trial [9], thus patients received 12 mg if baseline body weight was ≥60 kg or 8 mg if baseline body weight was < 60 kg, once daily orally. Atezolizumab plus bevacizumab was administered as described in the IMbrave150 trial, and all patients received 1200 mg of atezolizumab plus 15 mg/kg of body weight of bevacizumab intravenously every 3 weeks [10]. Sorafenib was administered as described in the SHARP and Asia Pacific trials, and all patients received 400 mg twice daily orally [11,12]. Regorafenib was administered as described in the RESORCE trial, and all patients received 160 mg once daily orally during weeks 1–3 of each 4-week cycle [3]. Cabozantinib was administered as described in the CELESTIAL trial, and all patients received 60 mg once daily orally [4]. Ramucirumab was administered as described in the REACH-2 trial, and all patients received 8 mg/kg of body weight intravenously every 2 weeks [5]. For patients who received second-line trans-arterial chemo-embolization (TACE), an emulsion of 5–20 ml lipiodol mixed with 20–60 mg pirarubicin was administered into the tumour-feeding vessels, followed by embolization with polyvinyl alcohol particles (90–500 μm) [13]. Treatment interruptions and/or dose reductions were allowed to manage adverse events. Response and progression to treatments were evaluated according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).

2.2. Statistical analysis

A frequency table was performed for categorical variables that were compared using Fisher's exact test. OS was defined as the time from the start date of the studied treatment to the date of death. OS was reported as median values expressed in months, with 95% confidence interval (CI). Univariate analyses were estimated using the product-limit method of Kaplan-Meier.

A p-value < 0.05 was considered statistically significant.

A MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

3. Results

3.1. Clinical characteristics and outcomes of the whole patient population

The overall cohort included 2225 consecutive patients from five countries between 9th July 2010 and 9th May 2022, of which 885 were treated with atezolizumab plus bevacizumab and 1341 with lenvatinib. A total of 1381 consecutive patients had progressive disease after first-line therapy and were available for the analysis. In first-line therapy, 917 patients (66.4%) were treated with lenvatinib, and 464 patients (33.6%) were treated with atezolizumab plus bevacizumab. The main characteristics of the study population are reported in Table 1. Patients receiving atezolizumab plus bevacizumab in first-line were most frequently of Western ethnicity (p < 0.01) and with a Child-Pugh (CP) score A

Table 1
Baseline characteristics of lenvatinib and atezolizumab plus bevacizumab first-line groups.

	Lenvatinib 917 (66.4%)	Atezolizumab + Bevacizumab 464 (33.6%)	p
Male	733 (79.9%)	377 (81.2%)	0.61
Female	184 (20.1%)	87 (18.7%)	
≤ 70	418 (45.6%)	194 (41.8%)	0.19
> 70	499 (54.4%)	270 (58.2%)	
Western	770 (83.7%)	450 (97.0%)	**< 0.01**
Eastern	147 (31.7%)	14 (3.0%)	
Viral	547 (59.6%)	244 (52.6%)	**0.01**
No viral	370 (40.3%)	220 (47.4%)	
At least one local therapy	741 (80.8%)	312 (67.2%)	**< 0.01**
No local therapy	176 (19.2%)	152 (32.7%)	
CP A	814 (88.8%)	428 (92.2%)	**< 0.05**
CP B	103 (11.2%)	36 (7.7%)	
BCLC B	371 (40.4%)	172 (37.1%)	0.24
BCLC C	546 (59.5%)	292 (62.9%)	
PS 0–1	906 (98.8%)	452 (97.4%)	0.07
PS > 1	11 (1.2%)	12 (2.6%)	
PVT	190 (20.7%)	116 (25.0%)	0.07
No PVT	727 (79.3%)	348 (75.0%)	
AFP < 400 ng/ml	621 (67.7%)	301 (64.9%)	0.30
AFP ≥ 400 ng/ml	293 (31.9%)	161 (34.7%)	
EHD	371 (40.4%)	176 (37.9%)	0.38
No EHD	546 (59.5%)	288 (62.1%)	
ALBI 1	813 (88.6%)	418 (90.1%)	0.57
ALBI 2	96 (10.5%)	44 (9.5%)	
NLR ≤ 3	468 (51.0%)	231 (49.8%)	**0.01**
NLR > 3	287 (31.3%)	197 (42.4%)	

AFP, alpha-feto-protein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CP, Child Pugh; EHD, extrahepatic disease; NLR, neutrophil-lymphocyte ratio; PS, performance status; PVT, portal vein thrombosis. p-values < 0.05 are shown in bold.

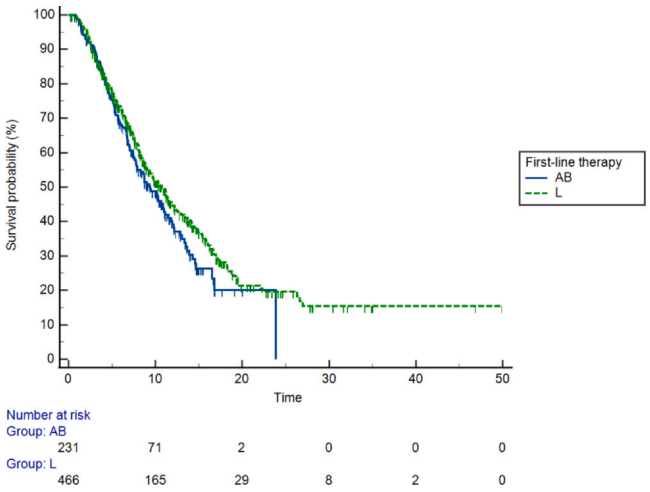

Fig. 1. Kaplan-Meier curves for overall survival in patients not-receiving second-line therapy after progressive disease to lenvatinib or atezolizumab plus bevacizumab first-line.

(p < 0.05). Patients receiving lenvatinib in first-line were most frequently with viral-cirrhosis (p = 0.01), with a previous locoregional procedure including surgery, TACE or radiofrequency (p < 0.01), and neutrophil-lymphocyte ratio (NLR) ≤ 3 (p = 0.01).

50.5% (697) of patients with progressive disease didn't receive second-line therapy, achieving a median OS of 10.3 months (95% CI: 8.9–11.2). 33.1% (231) of these patients had been treated with atezolizumab plus bevacizumab in first-line, while 66.8% (466) with lenvatinib. There was no significant difference in median OS between these two subgroups (p = 0.09; HR: 0.82, 95% CI: 0.66–1.03, reference group: atezolizumab plus bevacizumab). In particular, median OS in the lenvatinib group was 10.7 months (95% CI: 9.0–12.0) and median OS in the atezolizumab plus bevacizumab first-line group was 9.4 months (95% CI: 7.8–11.1) (Fig. 1).

49.5% (684) of patients with progressive disease received second-line therapy, achieving a median OS of 18.6 months (95% CI: 15.7–21.2). 34.1% (233) of these patients had been treated with atezolizumab plus bevacizumab in first-line, while 65.9% (451) with lenvatinib. There was no significant difference in median OS between these two subgroups (p = 0.12; HR: 0.80, 95% CI: 0.62–1.06, reference group: atezolizumab plus bevacizumab). In particular, median OS in the lenvatinib group was 20.6 months (95% CI: 16.1–22.8) and median OS in the atezolizumab plus bevacizumab first-line group was 15.7 months (95% CI: 14.5–17.0) (Fig. 2).

The main differences of patients receiving and not-receiving second-line therapy are reported in Table 2. Patients receiving second-line therapy after progressive disease were more frequently younger (p = 0.01) and presented more frequently with CP score A (p < 0.01), BCLC B disease (p < 0.01), and albumin-bilirubin 1 grade (p < 0.01). Patients not-receiving second-line therapy after progressive disease were more frequently of Eastern ethnicity (p < 0.01) and presented more frequently with portal vein thrombosis (p < 0.01), high levels of basal α-fetoprotein (p = 0.01), and NLR > 3 (p = 0.02).

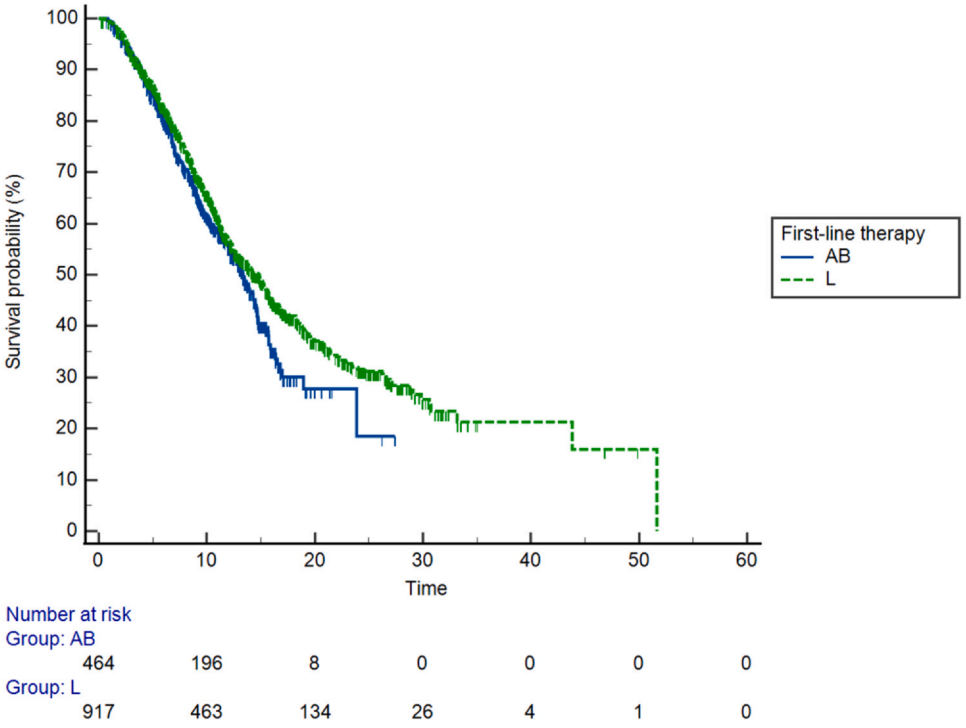

Fig. 2. Kaplan-Meier curves for overall survival in patients receiving second-line therapy after progressive disease to lenvatinib or atezolizumab plus bevacizumab first-line.

Table 2
Baseline characteristics of patients receiving and not-receiving second-line therapy.

	Second-line 684 (49.5%)	No second-line 697 (50.5%)	p
Atezolizumab plus Bevacizumab	233 (34.1%)	231 (33.1%)	0.73
Lenvatinib	451 (65.9%)	466 (66.8%)	
Male	559 (81.7%)	551 (79.0%)	0.22
Female	125 (18.3%)	146 (20.9%)	
≤ 70	333 (48.7%)	291 (41.7%)	**0.01**
> 70	351 (51.3%)	406 (58.2%)	
Western	625 (91.4%)	595 (85.4%)	**< 0.01**
Eastern	59 (8.6%)	102 (14.6%)	
Viral	404 (59.1%)	387 (55.5%)	0.19
No viral	280 (40.9%)	310 (44.5%)	
At least one local therapy	548 (80.1%)	505 (72.4%)	0.06
No local therapy	136 (19.9%)	162 (23.2%)	
CP A	639 (93.4%)	603 (86.5%)	**< 0.01**
CP B	45 (6.6%)	94 (13.5%)	
BCLC B	302 (44.1%)	241 (34.6%)	**< 0.01**
BCLC C	382 (55.8%)	456 (65.4%)	
PS 0–1	676 (98.8%)	682 (97.8%)	0.21
PS > 1	8 (1.2%)	15 (2.1%)	
PVT	126 (18.4%)	180 (25.8%)	**< 0.01**
No PVT	558 (81.6%)	517 (74.2%)	
AFP < 400 ng/ml	478 (69.9%)	444 (63.7%)	**0.01**
AFP ≥ 400 ng/ml	203 (29.7%)	251 (36.0%)	
EHD	256 (37.4%)	291 (41.7%)	0.11
No EHD	428 (62.6%)	406 (58.2%)	
ALBI 1	632 (92.4%)	599 (85.9%)	**< 0.01**
ALBI 2	47 (6.9%)	93 (13.3%)	
NLR ≤ 3	356 (52.0%)	341 (48.9%)	**0.02**
NLR > 3	214 (31.3%)	272 (39.0%)	

AFP, alpha-feto-protein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CP, Child Pugh; EHD, extrahepatic disease; NLR, neutrophil-lymphocyte ratio; PS, performance status; PVT, portal vein thrombosis. p-values < 0.05 are shown in bold.

91.4% (625) of patients receiving second-line therapy after progressive disease were of Western ethnicity, while 8.6% (59) of Eastern ethnicity. There was a significant difference in median OS between these two subgroups (p < 0.01; HR: 0.32, 95% CI: 0.19–0.54, reference group: Eastern). In particular, median OS in the Western group was 19.3 months (95% CI: 16.3–22.3) and median OS in the Eastern group was 12.1 months (95% CI: 9.7–14.7) (Fig. 3).

3.2. Clinical outcomes in patients receiving lenvatinib in first-line

In patients treated with lenvatinib in first-line, there was no significant difference in OS in the comparison of different second-line therapies (p = 0.27; sorafenib HR: 1; immunotherapy HR: 0.69, 95% CI: 0.45–1.05; other therapies HR: 0.85, 95% CI: 0.52–1.38). In particular, 181 (40.1%) patients were treated with sorafenib in second-line therapy achieving a median OS of 15.8 months (95% CI: 14.7–20.6); 59 (13.1%) patients were treated with immunotherapy (of which 26 (5.8%) with atezolizumab plus bevacizumab) not reaching a median OS; 45 (10.0%) patients received other second-line therapies with a median OS of 20.8 months (95% CI: 11.8–29.1). In particular, in this last subgroup, 15 (3.3%) patients received regorafenib, 26 (5.8%) received ramucirumab, and 4 (0.9%) patients received cabozantinib (Fig. 4). 166 (36.8%) patients underwent TACE as second-line treatment achieving a median OS of 24.7 months (95% CI: 19.3–29.8).

We then compared each second-line treatment with sorafenib which is the only therapy approved in patients progressed to lenvatinib in many countries. Patients who underwent TACE had a significative longer OS than those who received sorafenib in a second-line setting (p < 0.01; HR 0.64, 95% CI: 0.47–0.88, reference group: sorafenib) (Fig. 5A). No statistical differences were found in the direct comparison of sorafenib and immunotherapy subgroups (p = 0.10; HR: 0.71, 95% CI: 0.46–1.07, reference group: sorafenib) (Fig. 5B), and of sorafenib versus other second-line therapies (p = 0.51; HR: 0.85, 95% CI: 0.53–1.37, reference group: sorafenib) (Fig. 5C).

3.3. Clinical outcomes in patients receiving atezolizumab plus bevacizumab in first-line

In patients treated with atezolizumab plus bevacizumab in first-line, there was a significant difference in OS in the comparison of different second-line therapies (p < 0.01; sorafenib HR: 1; lenvatinib HR: 0.50, 95% CI: 0.27–0.90; cabozantinib HR: 1.29, 95% CI: 0.55–3.01; other therapies HR: 0.54, 95% CI: 0.29–1.03). In particular, 43 (18.4%) patients were treated with sorafenib in second-line therapy achieving a median OS of 14.2 months (95% CI: 8.8–15.7); 84 (36.0%) patients were treated with lenvatinib in second-line therapy with a median OS of 17.0 months (95% CI: 14.8–18.9); 23 (9.9%) patients received cabozantinib in second-line therapy achieving a median OS of 12.4 months (95% CI: 7.2–13.4); 56 (24.0%) patients received other second-line therapies not reaching a median OS. In particular, in this last subgroup, 3 (1.3%) patients received regorafenib, 14 (6.0%) received ramucirumab, 6 (2.6%) patients received immunotherapy, and 33 (14.2%) were treated with other unspecified second-line therapies (Fig. 6). 27 (11.6%) patients underwent TACE as second-line treatment achieving a median OS of 15.9 months (95% CI: 14.6–16.3).

We then compared each second-line treatment with sorafenib which is the only therapy approved in patients progressed to atezolizumab plus bevacizumab in many countries. Patients who received lenvatinib had a significative longer OS than patients treated with sorafenib in second-line setting (p = 0.01; HR: 0.45, 95% CI: 0.24–0.83, reference group: sorafenib) (Fig. 7A). Also, patients who underwent TACE had a significative longer OS than patients who received sorafenib in second-line setting (p < 0.05; HR 0.46, 95% CI:

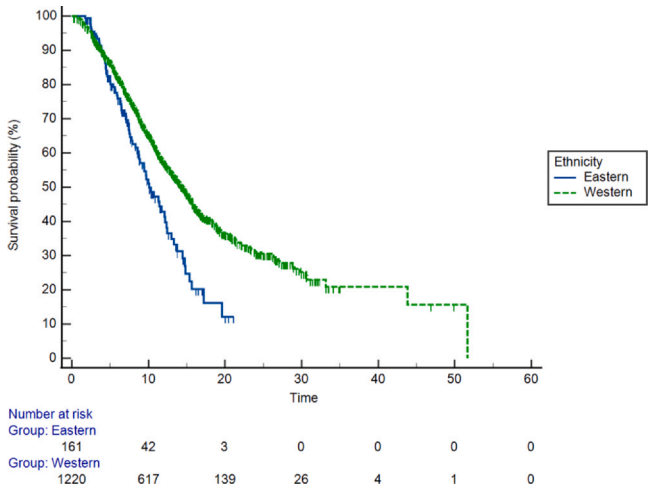

Fig. 3. Kaplan-Meier curves for overall survival in patients receiving second-line therapy according to ethnicity.

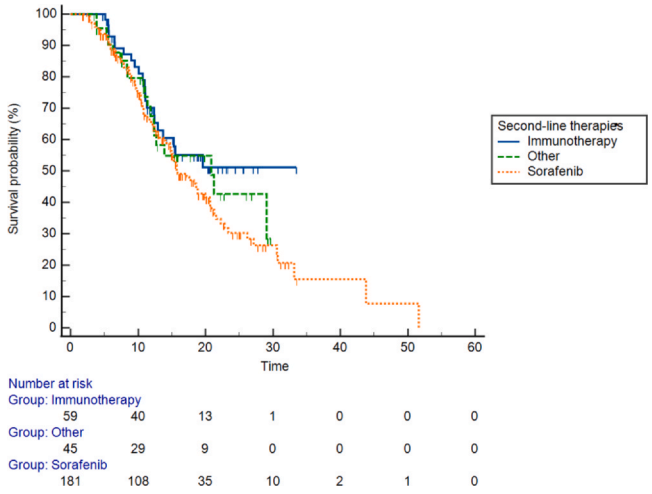

Fig. 4. Kaplan-Meier curves for overall survival in patients treated with different second-line therapies after progressive disease to lenvatinib.

0.22–0.99, reference group: sorafenib) (Fig. 7B). No statistical differences were highlighted in the direct comparison of sorafenib subgroup versus cabozantinib subgroup (p = 0.35; HR: 1.39, 95% CI: 0.69–2.81, reference group: sorafenib) (Fig. 7C), and of sorafenib subgroup versus other second-line therapies subgroup (p = 0.06; HR: 0.56, 95% CI: 0.30–1.03, reference group: sorafenib) (Fig. 7D).

The median OS reached by different second-line therapies after progressive disease to atezolizumab plus bevacizumab (A) or lenvatinib (B) are summarised in Fig. 8.

4. Discussion

This is the first large real-world study that compared different second-line therapies following the two currently most used first-line treatments in clinical practice in patients with advanced or intermediate-stage HCC. First, our study showed that approximately half of the patients who progressed to first-line treatment also received second-line therapies. These data are better than those reported in previous trials if we consider that only one third of patients treated with lenvatinib in the phase III REFLECT trial received second-line therapy [14]. Factors that could be associated with these results could be the excellent survival outcomes and the tolerability of these two first-line regimens [9,10]. Furthermore, the greater experience gained by clinicians in the management of these patients both in first-line and second-line setting can play a role in this finding. On the other hand, our analysis highlighted an excellent median OS for patients undergoing second-line therapy after progression to lenvatinib (20.6 months) or atezolizumab plus bevacizumab (15.7 months) without any statistically significant difference (p = 0.12).

Another interesting aspect to underline is that patients not-receiving second-line therapy reached a median OS of 10.3 months, with no significant difference depending on the first-line treatment (p = 0.09).

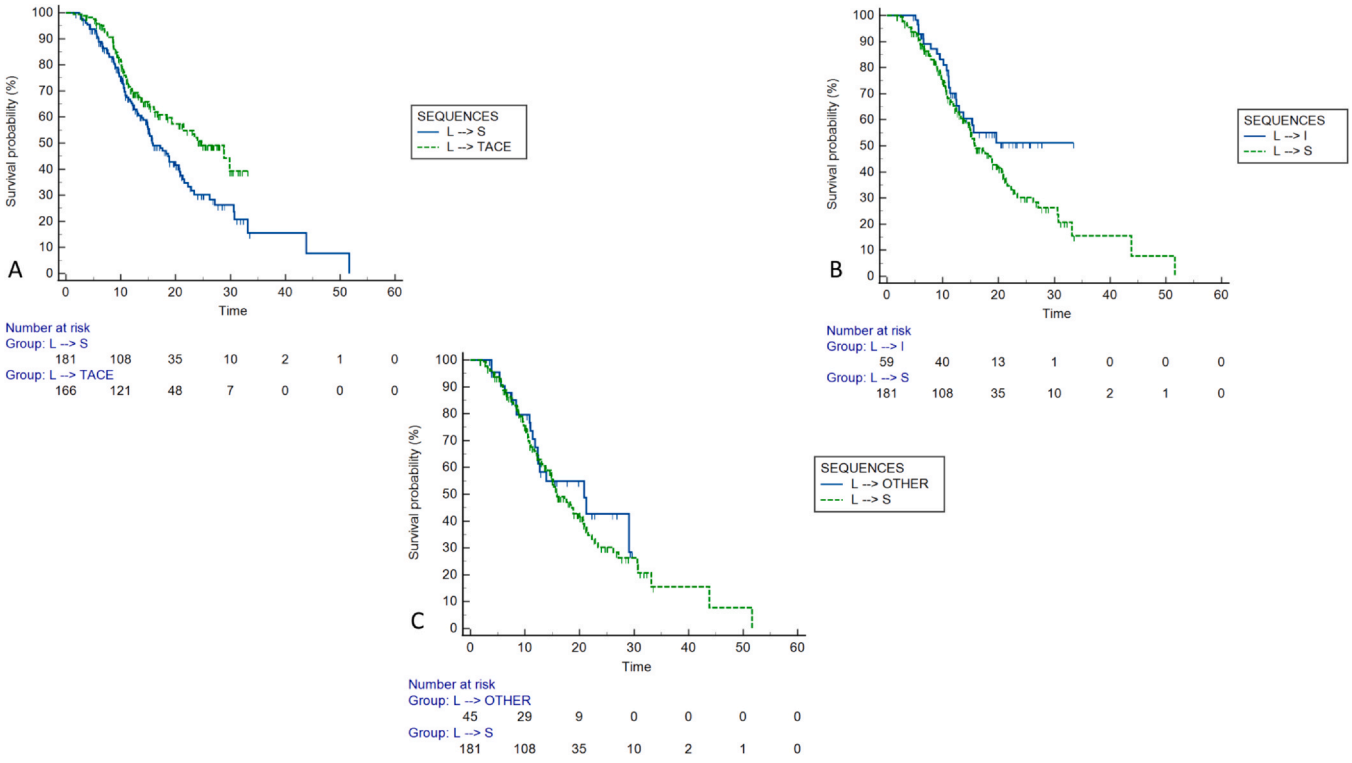

Fig. 5. Kaplan-Meier curves for overall survival (OS) in patients treated with trans-arterial chemo-embolization or sorafenib as second-line therapy after lenvatinib (A). Kaplan-Meier curves for OS in patients treated with immunotherapy or sorafenib as second-line therapy after lenvatinib (B). Kaplan-Meier curves for OS in patients treated with other treatments or sorafenib as second-line therapy after lenvatinib (C).

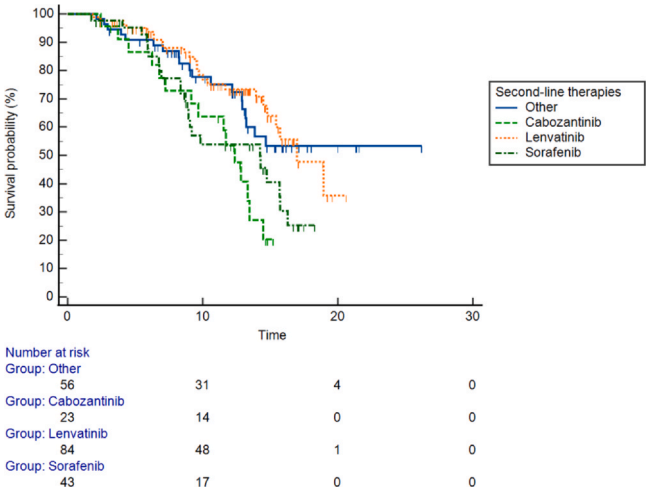

Fig. 6. Kaplan-Meier curves for overall survival in patients receiving second-line therapies after progressive disease to atezolizumab plus bevacizumab.

These patients are characterised by well-known negative prognostic factors for HCC, such as more advanced disease stage and worse liver function [8,15–21]. Moreover, our analysis confirms that other well-known parameters in this setting correlate with worse survival outcomes, including elevated baseline α-fetoprotein and NLR values [22–29]. On the other hand, it's noteworthy that patients not-receiving second-line therapy are more frequently older, probably due to the fact that other comorbidities associated with old age affected the possibility of accessing sequential treatments in our study population.

As regards patients receiving lenvatinib in first-line, the first data to underline is that the median OS achieved in our study population is comparable with that highlighted by the post hoc analysis of the phase III trial REFLECT on patients undergoing a second-line therapy after prior lenvatinib (20.8 months) [14]. Going into the specifics of the various second-line therapies received after lenvatinib, the patients with the best survival outcome were those treated with immunotherapy in second-line. This data is in line with the analysis conducted by Cabibbo and colleagues who used the Markov model to compare the results of randomised trials on first-line and second-line therapies currently available for HCC patients. In this analysis, patients treated with lenvatinib followed by second-line nivolumab or pembrolizumab were those with the longest median survivals, equal to 27 and 25 months, respectively [30]. The greater efficacy of using second-line immunotherapy after TKI first-line was also demonstrated by a network meta-analysis that compared data from the RESORCE, CELESTIAL, and CheckMate 040 trials, highlighting how the combination of nivolumab plus ipilimumab can achieve greater responses

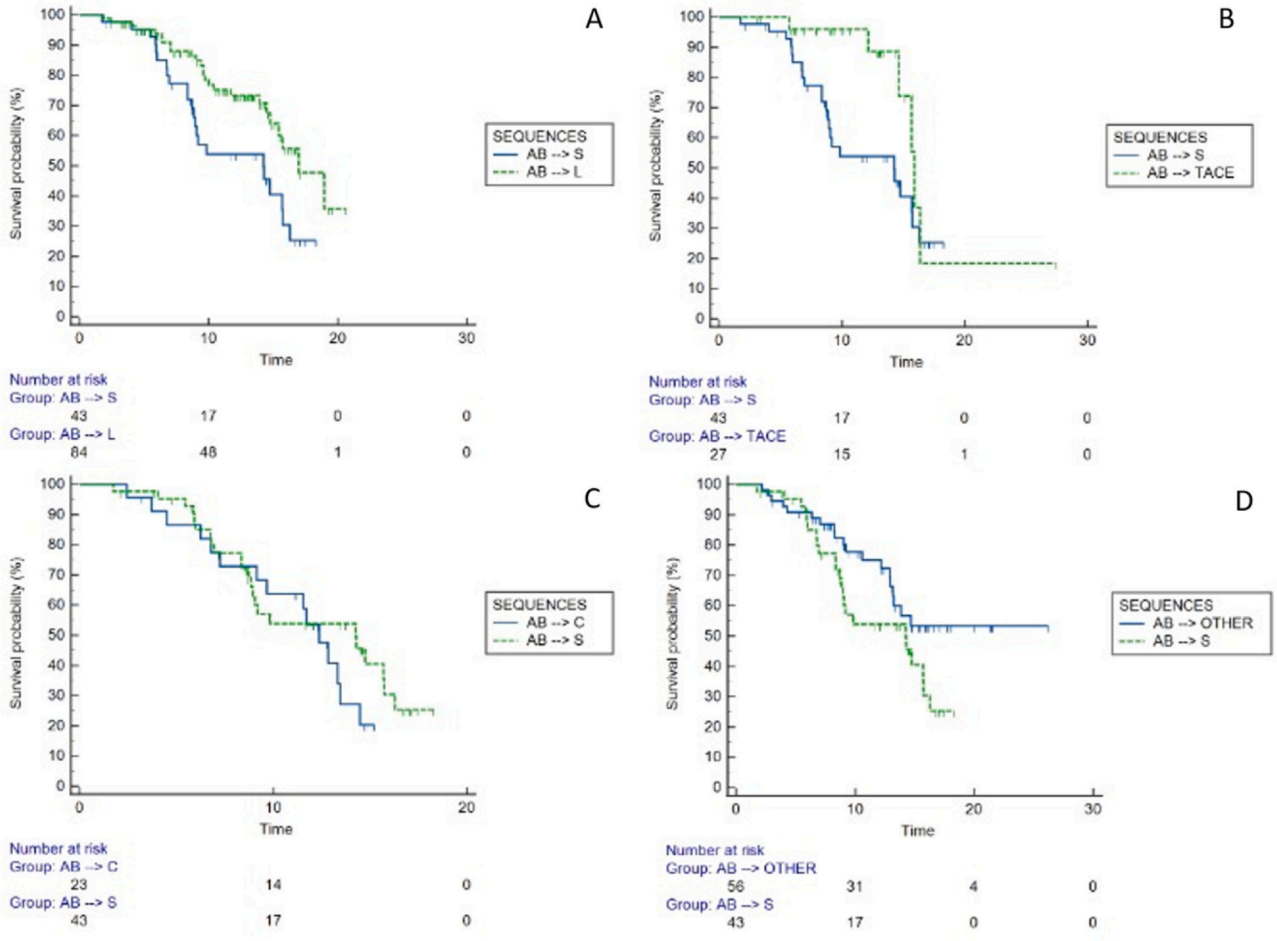

Fig. 7. Kaplan-Meier curves for overall survival (OS) in patients treated with lenvatinib or sorafenib as second-line therapy after atezolizumab plus bevacizumab (A). Kaplan-Meier curves for OS in patients treated with trans-arterial chemo-embolization or sorafenib as second-line therapy after atezolizumab plus bevacizumab (B). Kaplan-Meier curves for OS in patients treated with cabozantinib or sorafenib as second-line therapy after atezolizumab plus bevacizumab (C). Kaplan-Meier curves for OS in patients treated with other treatments or sorafenib as second-line therapy after atezolizumab plus bevacizumab (D).

than regorafenib and cabozantinib in this setting [31]. It should, however, be underlined that this better trend in terms of OS in favour of immunotherapy was lost in the direct comparison we conducted with patients treated with second-line sorafenib ($p = 0.10$). This controversial data may have been influenced by the sample difference between the two subgroups of patients and above all by the fact that the subgroup treated with immunotherapy is to be considered heterogeneous from a therapeutic point of view, as no data is available on which immunotherapy drugs (except for the 26 (5.8%) patients treated with atezolizumab plus bevacizumab) have been used. Randomised trials involving homogeneous populations from a therapeutic point of view are certainly needed to confirm these data and to clarify which immunotherapeutic drug or combination is more effective and safer in HCC patients progressed to first-line lenvatinib.

As regards the patients treated with atezolizumab plus bevacizumab first-line, the most important data that emerges is that the patients treated with lenvatinib second-line were those who achieved a better median survival, equal to 17.0 months. The statistically significant superiority of lenvatinib in this setting was also confirmed in direct comparison with second-line sorafenib-treated patients ($p = 0.01$). The efficacy of the use of TKIs after atezolizumab plus bevacizumab first-line had already been analysed by another Asian multicenter retrospective study which had demonstrated a statistically significant difference in favour of lenvatinib over sorafenib in terms of progression-free survival (PFS), but not in OS probably due to the low sample size (29 patients treated with the atezolizumab plus bevacizumab - sorafenib sequence and 19 with the atezolizumab plus bevacizumab - lenvatinib sequence) [32]. Our results are also confirmed in a second analysis based on the Markov model conducted by Cabibbo and colleagues who took into account the results deriving from randomised trials to compare the different therapeutic options available in the second-line setting after

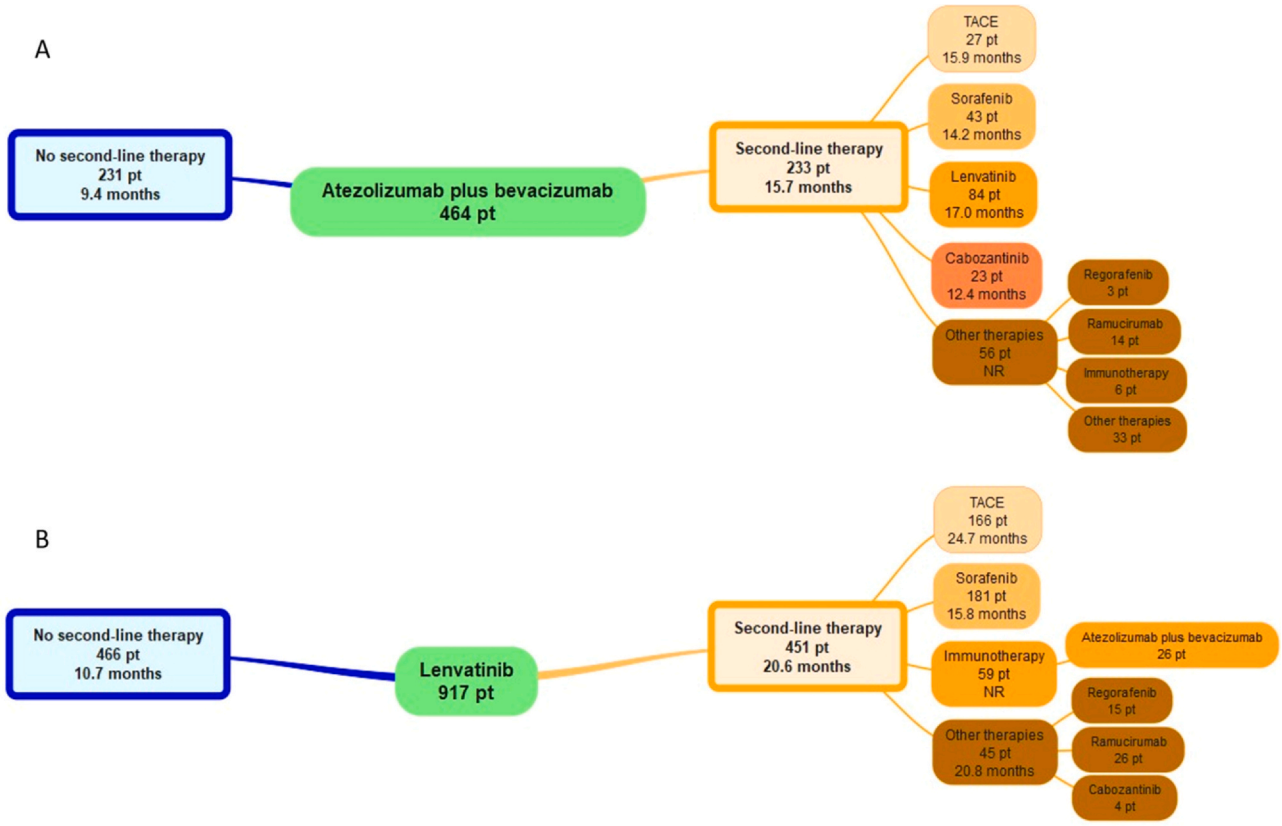

Fig. 8. Schematic diagrams of the study reporting the median overall survival reached by different second-line therapies after progressive disease to atezolizumab plus bevacizumab (A) or lenvatinib (B).

atezolizumab plus bevacizumab first-line. In this analysis, the atezolizumab plus bevacizumab – lenvatinib sequence was the best in terms of OS, reaching a median survival of 24.0 months [33].

Nowadays, the use of second-line TKIs after atezolizumab plus bevacizumab is a setting of great interest for clinicians, as data from randomised trials are not available. Only recently, a phase II trial on this topic evaluated the outcomes achieved by the use of second-line cabozantinib in patients treated with first-line immunotherapy. In this study, 19 patients who received the sequence of atezolizumab and bevacizumab – cabozantinib achieved a median OS of 14.3 months [34]. Another phase II study is underway, the REGONEXT trial, which will evaluate the survival outcomes obtained from the use of regorafenib in patients who have progressed to atezolizumab plus bevacizumab [35]. In our study, the atezolizumab plus bevacizumab - cabozantinib sequence was administered to 23 patients who achieved a median survival of 12.4 months. Only three patients, on the other hand, received the atezolizumab plus bevacizumab - regorafenib sequence, making the median OS analysis not significant.

Another setting of great interest currently concerns the use of immunotherapy in HCC patients progressed to previous immunotherapy. Initial evidence of the efficacy of immunotherapeutic sequences for the treatment of patients with HCC is available. Already in 2020, the analysis conducted by Cabibbo mentioned above demonstrated how the sequence atezolizumab plus bevacizumab - nivolumab can achieve a median survival of 24 months [30]. Subsequently, a retrospective real-world study showed how the use of the combination of nivolumab plus ipilimumab obtained a median survival of 10.9 months with a median time-to-progression of 2.96 months in patients previously treated with immunotherapy [36]. In our study, only six patients were treated with immunotherapy after atezolizumab plus bevacizumab, not allowing a reliable analysis of the median survival obtained. It is hoped that randomised trials will soon be undertaken with the aim to clarify which is the best second-line therapy both in terms of efficacy and quality of life in HCC patients who progressed to atezolizumab plus bevacizumab first-line treatment.

The data of our study concerning the outcomes obtained by patients undergoing TACE after first-line therapy deserve a separate discussion. After lenvatinib first-line, the median survival in this subgroup was 24.7 months, significantly longer than in the subgroup of patients treated with sorafenib second-line therapy (15.8 months, $p < 0.01$). Also, after atezolizumab plus bevacizumab first-line, the same significative difference in favour of patients treated with TACE compared to those treated with sorafenib was highlighted (15.9 months

versus 14.2 months, $p < 0.05$). These data are not so surprising, considering that most likely these were intermediate-stage patients who are the ones who benefit most from the use of locoregional therapies, such as TACE, and who present a better prognosis than advanced-stage patients [37]. It is known that patients classified as BCLC-B are an extremely heterogeneous population both in terms of tumour burden and in terms of residual liver function. Today, the guidelines indicate TACE as the treatment of choice for this population, but in clinical practice, this procedure is often not feasible also due to its detrimental effect on residual liver function [15]. On the other hand, both lenvatinib and atezolizumab plus bevacizumab have been shown to achieve an objective response in at least one third of patients treated both in the context of randomised phase III trials and in retrospective real-world studies [9,10,16–28,38,39]. Thanks to this significant objective response rate associated with the maintenance of good residual liver function, these two therapies are the first to obtain downstaging such as to allow access to locoregional procedures even HCC patients initially judged as unsuitable due to the high tumour burden [29,40–44].

Our study has many limitations, first of all, its retrospective nature which could not exclude selection bias, and not allowed us to know all the second-line therapies and the PFS achieved in this setting by all patients. Furthermore, we had available the baseline characteristics relating only to the setting prior to the first-line therapy and the follow-up protocol used did not provide for a centralised review, leaving the assessment of each patient's disease progression to the clinical practice of the single centre. However, it should be noted that this study represents the first large multicenter analysis of second-line therapies received by HCC patients after lenvatinib or atezolizumab plus bevacizumab first-line treatments. The high sample size makes it a valid proof-of-concept study and a useful starting point for understanding how best to design randomised trials in this setting.

5. Conclusion

In conclusion, this study demonstrates that approximately half of patients receiving first-line lenvatinib or atezolizumab plus bevacizumab access second-line treatment after progressive disease, without any statistical difference in OS. As regards patients eligible for locoregional procedures after first-line therapy, patients undergoing TACE achieve superior survival outcomes compared to sorafenib. In patients progressed to atezolizumab plus bevacizumab, the systemic therapy able to achieve the longest survival is lenvatinib. These are very interesting results that would be worth investigating also with randomised trials considering that in many countries the only therapy approved in this setting is sorafenib.

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CRediT authorship contribution statement

Mara Persano: Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Margherita Rimini**: Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Andrea Casadei-Gardini**: Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. All authors: Data curation, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A.C.G. is an advisor for AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, GSK, and MSD; received grants and personal fees from Bayer, Eisai, and MSD. M.S. is an advisor for AMGEN, Eisai, MERCK, MSD, and SERVIER. M.K. received research grant from AbbVie, Astellas Pharma, Bayer, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Medico's Hirata, MSD, Otsuka, Sumitomo Dainippon, Takeda, and Taiho; received advisory consulting fee from BMS, Chugai, Eisai, MSD, Ono pharmaceutical, and Taiho; received lecture fee from Bayer, Chugai, EA Pharma, Eisai, and MSD. The other authors declare no conflicts of interest.

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