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Second-line treatment patterns and outcomes in advanced HCC after progression on atezolizumab/bevacizumab

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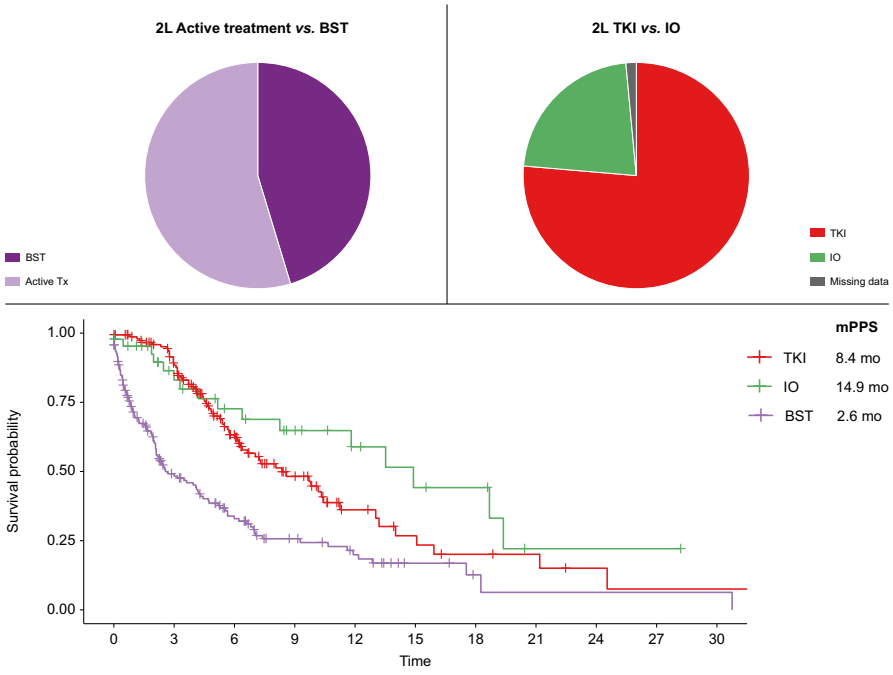
Graphical abstract



Highlights:

- ∼50% of patients progressing after atezolizumab plus bevacizumab continued treatment.
- Outcomes improved in patients continuing active treatment *vs.* those receiving best supportive care.
- Active treatments included both second-line tyrosine kinase inhibitors and immunotherapy.

Impact and implications:

There is currently a lack of level 1 data on second-line treatment options for patients with advanced hepatocellular carcinoma who progress after frontline atezolizumab plus bevacizumab, as all second-line approvals were established during the frontline sorafenib era. Our study aims to fill in some of the knowledge gap by investigating real-world patient outcomes in the second-line treatment setting. Findings from this study show that patients who continued active treatment had improved post-progression survival compared to those who received best supportive care, and medication regimens incorporating tyrosine kinase inhibitors as well as immunotherapy agents were active. These results can help inform clinicians of possible treatment options for patients who progress after frontline atezolizumab plus bevacizumab while we await maturing data from randomized-controlled trials.

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Second-line treatment patterns and outcomes in advanced HCC after progression on atezolizumab/bevacizumab☆

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Background & Aims: Atezolizumab/bevacizumab (A/B) is now a standard first-line treatment for advanced hepatocellular carcinoma (HCC), but the optimal second-line regimen is not known. We evaluated real-world treatment patterns and outcomes to investigate factors associated with post-progression survival (PPS).

Methods: In this multicenter, international, retrospective study, we examined clinical characteristics and outcomes of patients with advanced HCC who progressed on first-line A/B. The primary outcome of PPS was defined as time from first radiographic progression on A/B to death.

Results: A total of 406 patients alive after progression on first-line A/B were included in the final analysis, of whom 45.3% (n = 184) received best supportive treatment (BST) and 54.7% (n = 222) continued active systemic treatment. In the second line, 155 patients were treated with tyrosine kinase inhibitors (TKIs), 45 with immune checkpoint inhibitor (IO)-based regimens, and 3 had missing data. Median PPS of the whole cohort (mPPS) was 6.0 months (95% CI 5.2-7.2). On multivariate Cox regression analysis, absence of portal vein tumor thrombus, ECOG <2, and continued active treatment were predictors of better PPS. mPPS was significantly longer for patients who continued active treatment *vs.* BST (9.7 *vs.* 2.6 months; HR 0.41, p <0.001). In the second-line setting, patients treated with TKIs had a numerically shorter mPPS compared to those treated with IO (8.4 *vs.* 14.9 months; HR 1.37, p = 0.256).

Conclusions: Continuation of active therapy after A/B progression was independently associated with better survival even after adjusting for baseline disease characteristics. mPPS with IO-based therapy exceeded a year, suggesting that IO continuation post-progression may retain benefit. The precise sequencing of TKI and IO regimens warrants further investigation.

Introduction

The treatment paradigm for advanced or unresectable hepatocellular carcinoma (HCC) has shifted significantly since immune checkpoint inhibitor (IO)-based regimens such as atezolizumab plus bevacizumab (atezo/bev) and durvalumab plus tremelimumab were able to demonstrate superior outcomes over sorafenib in the frontline setting.[1,2] With new therapeutic advances, however, also come new questions and challenges. Since therapies currently approved for advanced HCC in the second-line (2L) setting were studied in the context of patients who received first-line (1L) sorafenib, the optimal management of patients who progress on first-line IO-based regimens such as atezo/bev is not defined, leading to uncertainty in clinical practice. In this study, we evaluated 2L treatment selections and clinical outcomes of patients with advanced or unresectable HCC who had disease progression while receiving atezo/bev, with the aim of better elucidating factors associated with post-progression survival.

Patients and methods

This was a retrospective, multicenter study investigating real-world patient characteristics and outcomes from an international HCC database comprised of information from patients treated at 22 centers across Europe, Asia, and North America. All patients were 18 years of age or older, had radiographic or histologic diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria,[3] and had

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unresectable or advanced HCC based on BCLC (Barcelona Clinic Liver Cancer) criteria.[4] We identified patients who were treated with 1L atezo/bev. From this population, we selected patients who had progression of disease during atezo/bev treatment; patients who died while on atezo/bev therapy were excluded. Post-progression survival (PPS) was defined as time of first radiographic progression on atezo/bev to death. Overall survival (OS) was defined as time from atezo/bev start to death. Progression-free survival (PFS) was defined as time from start of atezo/bev to first radiological evidence of progression or death, whichever occurred first. Treatment beyond progression was defined as therapy given more than 21 days, *i.e.* one cycle length, from first evidence of radiological progression and last dose of atezo/bev. Baseline patient characteristics were reported as median (IQR) for continuous variables and as n (%) for categorical variables. Chi-squared and Mann-Whitney tests were used to compare categorical and continuous variables, respectively. The Kaplan-Meier method was used to estimate median survivals and 95% CIs. Median survivals were compared using univariate Cox regression analysis, and variables that were associated with a p value <0.10 in the univariate model were included in multivariate analysis. Univariate and multivariate Cox regression analyses were performed to assess the impact of baseline patient demographics and disease characteristics on PPS. To reduce the risk of selection bias between those receiving active treatment and those prescribed best supportive treatment (BST) in the 2L, we performed propensity score matching (PSM) for the following confounding variables: Eastern Cooperative Oncology Group (ECOG) performance status at atezo/bev discontinuation, presence of portal vein tumor thrombosis (PVTT), Child-Pugh score, and best response to atezo/bev between the two groups. To perform the matching, we employed a PSM with 1:1 ratio and caliper of 0.2.

The study was conducted in accordance with ethical considerations from the Declaration of Helsinki. Ethical approval to conduct this study was granted locally by the institutional review board of each participating site. Informed consent was not considered necessary by the institutional review boards due to the retrospective nature of the study.

Results

A total of 840 patients treated with atezo/bev between May 2018 and November 2022 were identified in the AB-Real dataset.[5] The respective median OS and PFS of the whole population were 15.7 (95% CI 14.2-17.2) and 7.1 (95% CI 6.2-8.0) months. Of the 840 patients treated with atezo/bev, 389 patients were excluded either because they had received atezo/bev as 2L or later treatment or because they had not yet experienced progression on atezo/bev. Four hundred and fifty-one patients had progressed on treatment, of whom 45 patients had died and were excluded. The remaining 406 patients who were alive after progression on atezo/bev were included in the final analysis (Fig. 1). Among these patients, the median PFS was 3.4 months (95% CI 3.0-3.9) on first-line atezo/bev. Six patients remained on atezo/bev post-progression, while for the remaining 400 patients, reasons to stop atezo/bev were as follows: radiological progression (n = 322), clinical deterioration (n = 36), toxicity (n = 25), completion of treatment plan (n = 3), and unknown (n = 14).

Patient characteristics

Baseline characteristics of the overall cohort are shown in Table 1. Patients had a median age of 67 and the majority were male; 72% of patients were staged BCLC C, and 78.6% had Child-Pugh class A hepatic function. Most patients had a viral etiology of HCC. On atezo/bev, 57% of patients had disease control, which was defined as achieving a best response of complete response, partial response, or stable disease.

Best supportive treatment *vs.* active treatment

Within the analyzed cohort, 184 patients (45.3%) received BST and 222 patients (54.7%) continued active systemic treatment after progression (Table 1). Compared to patients who received BST, patients who continued treatment were younger, had higher proportion of Child-Pugh class A hepatic function, lower proportion of PVTT, better performance status at time of progression, higher proportion of extrahepatic disease, higher proportion of disease control while on atezo/bev, and were more likely to have viral etiology of HCC.

Post-progression treatment

Among patients who continued active treatment, 203 patients received one further treatment line after atezo/bev, 12 received two more lines, and 5 received three or more. The median time from end of 1L therapy to start of 2L treatment was 0.79 months (IQR 0.66-1.32). As shown in Fig. 1, in the 2L setting, 155 patients were treated with single-agent tyrosine kinase inhibitors (TKIs), 45 with IO-based regimens, and 3 had missing treatment data. Among single-agent TKI-treated patients, 75 received sorafenib, 71 lenvatinib, and 9 cabozantinib; among IO-treated patients, 8 received ipilimumab plus nivolumab (ipi/nivo), 6 atezo/bev beyond progression, 8 IO plus TKI, 8 IO monotherapy, and 15 unspecified IO-based therapy. The median duration of 2L treatment was 2.2 months (95% CI 1.9-2.8).

Post-progression outcomes in the overall cohort and subgroups

With a median follow-up of 7.5 months since progression on atezo/bev, 258 patients out of the overall cohort of 406 patients had died. Median PPS (mPPS) after 1L atezo/bev was 6.0 months (95% CI 5.2-7.2) for the overall cohort. In the active treatment group, mPPS was 9.7 months (95% CI 7.3-11.1) *vs.* 2.6 months (95% CI 2.1-4.4) in the BST group (HR: 0.41; 95% CI 0.32-0.54, p <0.001) (Fig. 2A). On univariate Cox regression analysis, female sex, Child-Pugh class A, absence of PVTT, ECOG <2 at time of progression on atezo/bev, disease control while on atezo/bev, and continued active treatment were associated with improved PPS. On multivariate analysis, absence of PVTT, ECOG <2, and continued active treatment remained independent predictors of a better PPS outcome (Table 2). Patients who received TKI-based treatment had a numerically shorter mPPS compared to those treated with IOs (8.4 *vs.* 14.9 months, HR 1.37, p = 0.26), although this finding was not statistically significant. Fig. 2B shows the Kaplan-Meier curve for PPS for patients who received BST *vs.* IO *vs.* TKI in the 2L setting. Among patients who received 2L TKIs, treatment with lenvatinib led to a numerically longer mPPS compared with sorafenib, which trended towards significance (10.2 *vs.* 7.0 months, HR 0.61, 95% CI 0.37-1.01, p = 0.05).

When the analysis was restricted to patients who stopped first-line atezo/bev due to radiological progression or clinical deterioration (n = 358), mPPS was 5.8 months (95% CI 4.9-7.0). Median PPS for active treatment *vs.* BST (9.7 *vs.* 2.4 months, HR 0.4, 95% CI 0.29-0.50) and TKI *vs.* IO therapy (8.4 months [95% CI 6.32-11.25] *vs.* 14.9 months [95% CI 11.81-NA]) were similar or unchanged compared to those from the overall cohort.

Out of the 173 (43%) patients who had progressive disease as best response to first-line atezo/bev, approximately half (n = 89) received further systemic therapy. Sixty six received TKIs, 19 IO-based therapies, and 4 had missing treatment data. There was no statistically significant difference between the mPPS for TKI-treated *vs.* IO-treated (8.6 *vs.* 11.7 months, p = 0.33) patients.

Outcomes in the propensity score-matched cohort

After performing PSM for confounding variables (ECOG score at time of progression on atezo/bev, presence of PVTT, Child-Pugh score, and disease control rate during atezo/bev), continuation of active treatment retained its association with longer mPPS compared to BST (8.6 *vs.* 2.5 months, HR 0.4, 95% CI 0.28-0.58, p <0.001). Fig. 3 shows the Kaplan-Meier curves for PPS after PSM, stratified by the receipt of active treatment *vs.* BST (Fig. 3A), and by the type of treatment (Fig. 3B). After PSM, patients who received 2L TKI regimens again had a numerically shorter but statistically nonsignificant mPPS compared to those treated with IOs (8.1 *vs.* 11.7 months, HR 1.22, 95% CI 0.57-2.61, p = 0.60).

Discussion

The regulatory approvals in recent years of atezolizumab plus bevacizumab as well as durvalumab plus tremelimumab have dramatically altered the treatment paradigm for advanced and unresectable HCC and generated considerable excitement at the promise of improved outcomes in this aggressive malignancy.[1,4] However, the management of patients who progress on 1L IO-based regimens has arisen as a new therapeutic challenge and area of unmet investigational need. Given the lack of data from randomized-controlled trials within this realm, there are currently no evidence-based recommendations on treatment selection after progression on 1L IO, and patients who progress after atezo/bev or durvalumab plus tremelimumab are encouraged to enroll in clinical trials.[3,6] We reported here data from patients treated at multiple centers

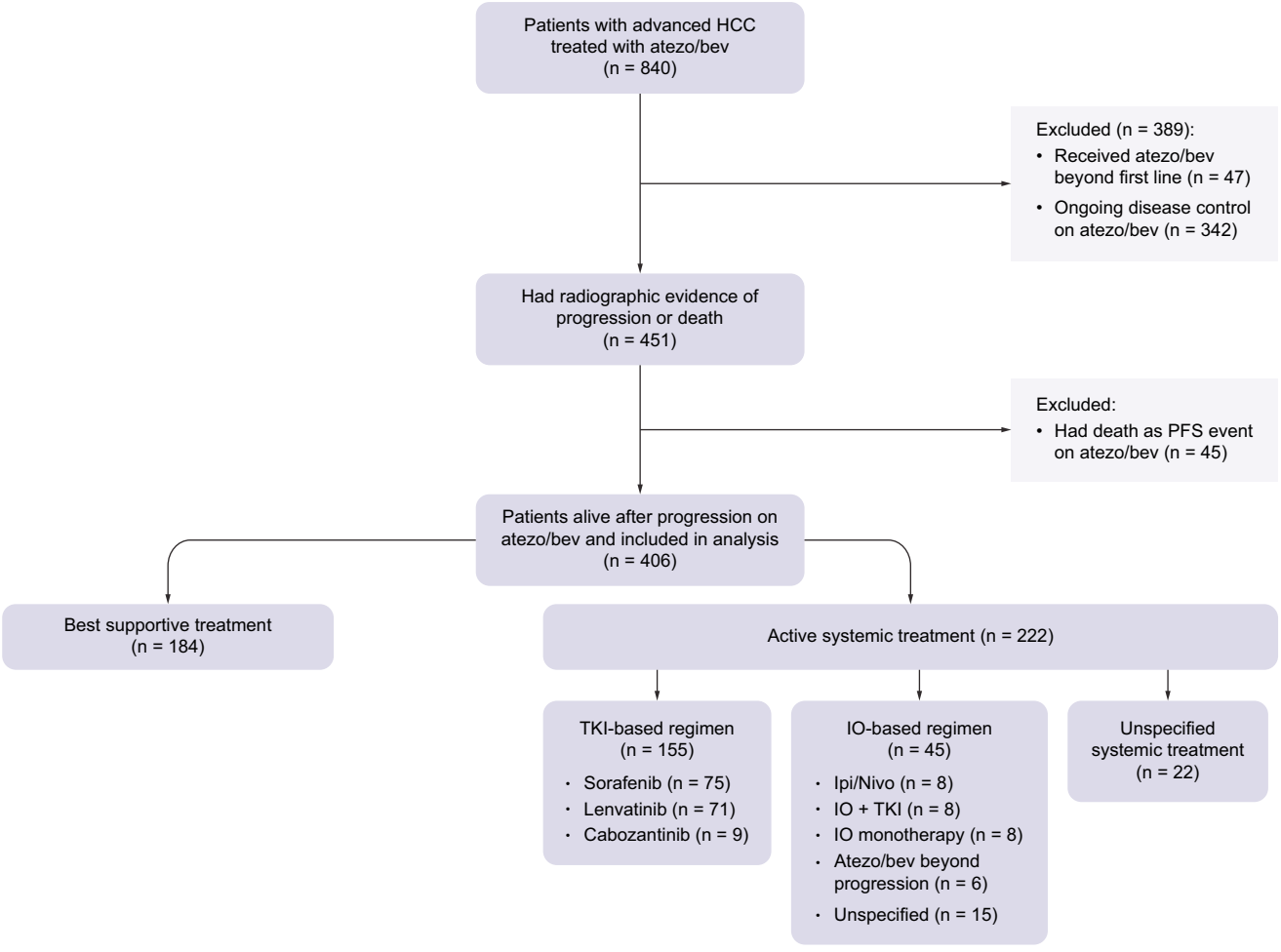

Fig. 1. Patient flowchart. HCC, hepatocellular carcinoma; IO, immune checkpoint inhibitor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Table 1. Baseline patient characteristics in overall population, active treatment group, and BST group.

Characteristic	Overall population (n = 406)	Active systemic treatment (n = 222)	Best supportive treatment (n = 184)	*p* values
Age – median (IQR)	67 (59-73)	64 (57-61)	69 (61-67)	0.01*
Male sex – n (%)	330 (81.4%)	181 (81.8%)	146 (79.2%)	0.3
Geographic location - n (%)				0.72
Europe	127 (31.3%)	59 (26.6%)	68 (37.0%)	
North America	109 (26.8%)	43 (19.4%)	66 (35.9%)	
Asia	170 (41.9%)	120 (54.0%)	50 (27.1%)	
BCLC stage – n (%)				0.054
A	12 (2.9%)	3 (1.3%)	10 (5.6%)	
B	102 (25.1%)	57 (25.8%)	46 (24.7%)	
C	292 (72%)	162 (72.9%)	128 (69.7%)	
AFP – median (range)	118 (10-2,520)	104 (9-1,964)	131 (12-3,520)	0.235
Child-Pugh class – n (%)				0.001*
A	319 (78.6%)	184 (82.7%)	133 (72.4%)	
B	82 (20.3%)	37 (16.9%)	47 (25.3%)	
C	5 (1.1%)	1 (0.4%)	4 (2.3%)	
Cirrhosis – n (%)	306 (78.6%)	169 (76.9%)	143 (77%)	0.541
Ascites – n (%)	102 (25.1%)	54 (24.4%)	56 (30.3%)	0.113
HCC etiology – n (%)				<0.001*
HBV	130 (31.9%)	88 (39.6%)	40 (21.9%)	
HCV	112 (27.7%)	55 (24.9%)	56 (30.3%)	
Non-viral	164 (40.4%)	79 (35.5%)	88 (47.8%)	
Portal vein tumor thrombus – n (%)	134 (33%)	58 (26.2%)	76 (41.6%)	0.003*
Extrahepatic sites – n (%)	189 (46.5%)	119 (53.8%)	68 (36.8%)	0.001*
ECOG score (initial) – n (%)				0.341
<2	393 (96.7%)	216 (97.3%)	176 (95.5%)	
≥2	13 (3.3%)	6 (2.7%)	8 (4.5%)	
ECOG score (at progression of disease) – n (%)				<0.001*
<2	260 (64%)	183 (82.3%)	75 (40.9%)	
≥2	70 (17.3%)	17 (7.7%)	91 (49.5%)	
Best response to atezo/bev – n (%)				<0.001*
CR	21 (5.2%)	4 (1.8%)	15 (8.1%)	
PR	62 (15.3%)	20 (9%)	21 (11.2%)	
SD	148 (36.6%)	107 (48.2%)	50 (27.3%)	
PD	174 (42.9%)	91 (41%)	98 (53.4%)	

Some sections do not sum to 100% due to missing data.
AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; HCC, hepatocellular carcinoma; PD, progressive disease; PR, partial response; SD, stable disease.
*Statistically significant p <0.05. The level of significance was estimated by using Chi-squared and Mann-Whitney test for categorical and continuous variables, respectively.

across three continents in order to offer insight into current real-world practice patterns.

In our study, patients treated with 1L atezo/bev had OS and PFS outcomes comparable with those reported in the IMbrave150 study.[1,7] Among patients who received 2L treatment, the majority (76%) were started on TKI monotherapy. Patients switched to TKIs were generally treated with either sorafenib or lenvatinib, both multikinase inhibitors that initially gained regulatory approval for use in the 1L setting but now are increasingly utilized as subsequent line treatments.[3,6,8] Prior to the availability of real-world data, a study that constructed a Markov model to estimate survival outcomes for patients treated with 2L TKIs or ramucirumab after progression on atezo/bev predicted that lenvatinib or sorafenib would be most effective.[9] Several observations from pharmacokinetics and cellular signaling studies offer insight into the rationale for use of TKIs in the post-IO setting. Monoclonal antibodies, including PD-(L)1 inhibitors, persist in the body for multiple weeks after initial infusion.[10] TKI therapy may therefore have a synergistic effect with previous IO even when given sequentially. Additionally, patients who progress on atezo/bev therapy display either primary or acquired resistance to anti-PD-(L)1 therapy, the mechanisms of which potentially include immune dysfunction within the tumor microenvironment, T-cell exclusion, or lack of PD-L1.[11] In patients with HCC specifically, *CTNNB1* mutation leading to WNT/β-catenin pathway activation has been associated with primary anti-PD-(L)1 resistance via T-cell exclusion.[12] In the setting of combination IO and anti-angiogenic agent failure, multikinase inhibitors can offer alternative antitumor mechanisms that are not dependent on an immunocompetent tumor microenvironment, such as targeting signaling pathways associated with cell proliferation.[13–15] Patients treated with 2L TKIs in our study had a median PPS of 6.0 months, suggesting that TKIs remain active therapies after progression on atezo/bev. Prospective evidence for this includes findings from a phase II trial that investigated the efficacy of cabozantinib after progression on 1-2 prior lines of therapy, with one line including IO. Among 13 patients who received 1L atezo/bev, 2L cabozantinib yielded a median PFS of 4.3 months and median OS of 9.9 months.[16]

Interestingly, patients in our study treated with lenvatinib had a longer PPS compared to those treated with sorafenib. Preclinical studies have shown that lenvatinib demonstrates more potent anticancer activity in immunocompetent mouse models compared to sorafenib and exhibits immunomodulatory activity that synergizes with anti-PD-(L)1 therapy.[17,18] In a retrospective study of 71 patients treated with 1L atezo/bev,

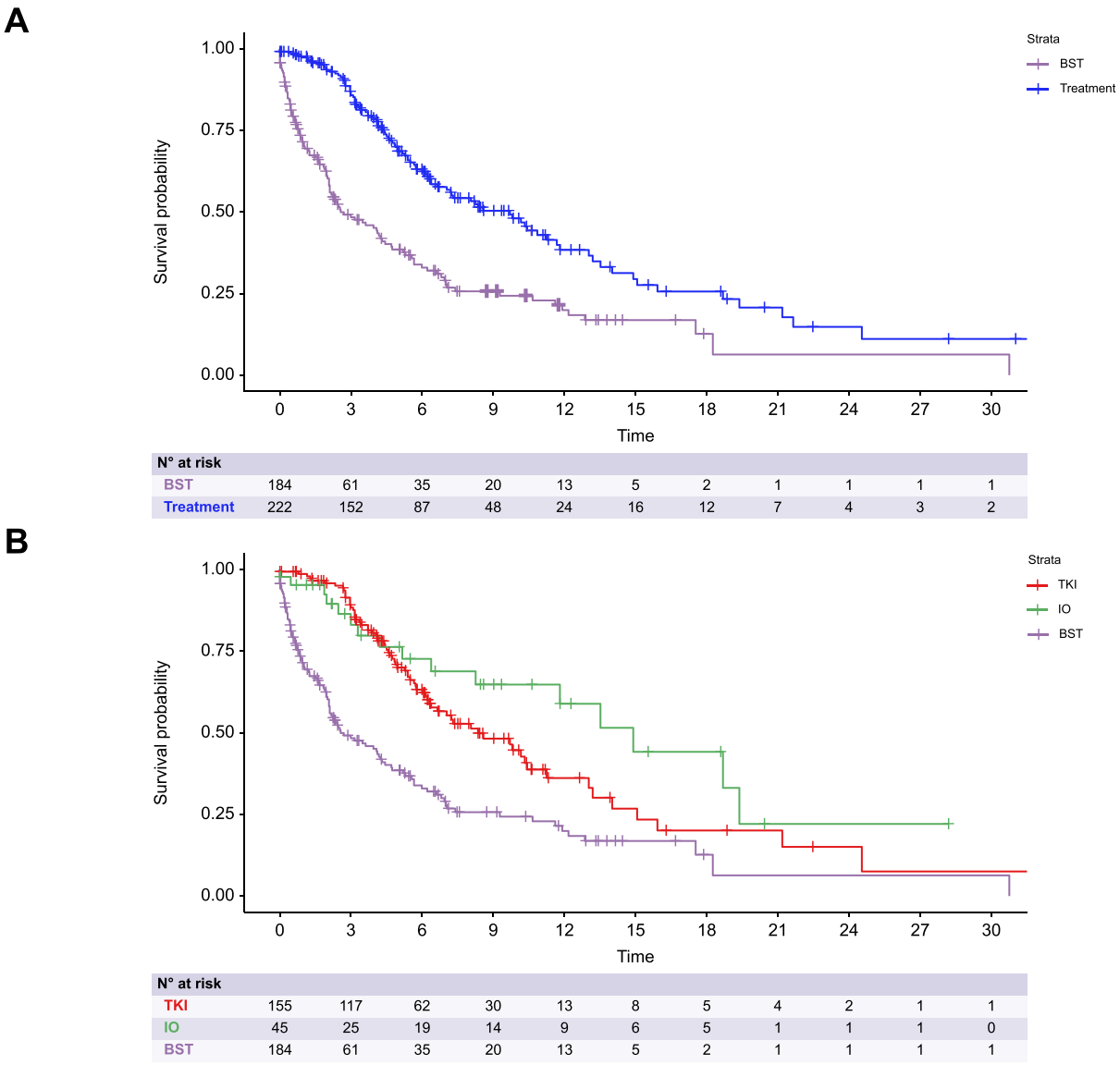

Fig. 2. Kaplan-Meier curves of PPS according to type of second-line treatment. Median survivals and confidence intervals were estimated using the Kaplan-Meyer method. (A) BST *vs*. active treatment; (B) BST *vs*. TKI *vs*. IO. BST, best supportive treatment; IO, immune checkpoint inhibitor; PPS, post-progression survival; TKI, tyrosine kinase inhibitor.

patients who received 2L lenvatinib had a significantly longer PFS compared to those who received sorafenib, although OS did not differ.[19] Further investigations are warranted to better elucidate the role of TKI sequencing and agent selection in light of these findings.

After progression on a previous IO agent, it remains an open question whether a role exists for IO continuation, which can take the form of either combining CTLA-4 blockade with an PD-(L)1 agent or switching to a different PD-(L)1 agent with or without a TKI partner. Interestingly, the 45 patients who received 2L IO regimens in our study had a numerically longer, although statistically nonsignificant, mPPS compared to patients who received 2L TKIs, suggesting that IO continuation may remain an option for patients who progress on atezo/bev. The rationale for the addition of an anti-CTLA-4 agent such as ipilimumab to PD-(L)1 therapy is enhanced antitumor efficacy in settings of primary anti-PD-(L)1 resistance via mechanisms distinct to combination therapy, such as greater expansion of activated $CD8^+$ T cells over phenotypically exhausted $CD8^+$ T cells, allowing for greater $CD8^+$ T-cell tumor infiltration compared to that seen in anti-PD-(L)1 monotherapy.[20,21] Efficacy from using combination PD-(L)1/CTLA-4 blockade as a way to reverse anti-PD-(L)1 resistance has been reported in three prospective trials in advanced melanoma.[21–23] The largest of these, SWOG S1616, showed a statistically significant improvement in PFS for patients with metastatic melanoma who progressed on 1L anti-PD-1 therapy and then received 2L ipi/nivo (6-month PFS 34%) compared to ipi alone (6-month PFS: 13%), as well as respective objective response rates of 28% *vs.* 9%.[21]

Table 2. Univariate and multivariate Cox regression analyses of factors associated with PPS.

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***p* values**	**HR**	**95% CI**	***p* values**
Treatment type: IO *vs.* BST	**0.26**	0.16-0.44	<0.001	**0.33**	0.20-0.57	<0.001
Treatment type: TKI *vs.* BST	**0.32**	0.24-0.43	<0.001	**0.41**	0.31-0.58	<0.001
Age (median)	1	0.99-1.01	0.844			
Sex (F *vs.* M)	**0.74**	0.55-0.99	0.045	0.78	0.56-1.04	0.163
BCLC (C *vs.* A or B)	1.17	0.87-1.59	0.295			
AFP (median)	1.21	0.92-1.59	0.168			
Child-Pugh score B/C *vs.* A	**1.49**	1.04-2.13	0.031	1.28	0.88-1.85	0.199
Cirrhosis (Y *vs.* N)	1.11	0.66-1.22	0.504			
Ascites (Y *vs.* N)	1.19	0.87-1.64	0.274			
Etiology (Non-viral *vs.* viral)	1.09	0.82-1.43	0.556			
PVTT (Y *vs.* N)	**1.5**	1.20-1.89	<0.001	**1.68**	0.59-1.24	<0.001
ECOG ≥2 *vs.* <2	**1.43**	2.99-5.85	<0.001	**3.09**	2.15-4.45	<0.001
ECOG ≥2 *vs.* missing	0.74	1.35-1.11	0.142	1.05	0.99-2.16	0.848
EHS (Y *vs.* N)	0.85	0.65-1.12	0.248			
Best response to A+B (CR/PR/SD *vs.* PD)	**1.47**	1.12-1.92	0.005	0.84	0.57-1.23	0.36
PFS (Below median *vs.* above)	1.27	0.97-1.67	0.078	1.46	0.99-2.16	0.056

Bolded variables were statistically significant p <0.05. The level of significance was estimated by using Chi-squared and Mann-Whitney test for categorical and continuous variables, respectively.

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BST, best supportive treatment; CR, complete response; EHS, extrahepatic spread; HR, hazard ratio; IO, immune checkpoint inhibitor; PD, progressive disease; PPS, post-progression survival; PR, partial response; PVTT, portal vein tumor thrombus; SD, stable disease; TKI, tyrosine kinase inhibitor.

The evidence for switching to a different PD-(L)1 agent with or without a TKI partner is less clear. From a pharmacokinetic perspective, atezolizumab is known to be more immunogenic compared to other anti-PD-(L)1 agents, with 29.6% of patients in the IMbrave150 study developing antidrug antibodies.[24] This is in contrast to other IO therapies when studied as single agents, which have reported antidrug antibody incidences ranging from 0–12.7%.[25] A higher antidrug antibody level has been associated with worse outcomes in patients with advanced HCC receiving atezo/bev;[26] conversely, switching to an alternative IO agent with lower immunogenicity may be one mechanism by which antitumor efficacy is enhanced. In a single-arm, prospective trial, 68 patients who had progressed on 1L atezo/bev were started on regorafenib plus pembrolizumab, a regimen which showed modest activity with an overall response rate of 5.9%, stable disease rate of 48.5%, and median PFS of 2.8 months.[27] A retrospective study examined 58 IO-treated patients with HCC who were rechallenged with another IO regimen, including 72% who received IO plus TKI or anti-VEGF therapy. They found an objective response rate of 26% and disease control rate of 55% in this population with similar rates of treatment-related adverse events between the two IO regimens, suggesting that IO rechallenge could be a safe and active treatment option.[28] On the other hand, in metastatic renal cell carcinoma the phase III CONTACT-03 trial comparing atezo/cabozantinib after progression on an IO regimen *vs.* cabozantinib alone resulted in negative findings. Patients randomized to atezo/cabozantinib had increased adverse events and no improvement in clinical outcomes compared to those randomized to cabozantinib monotherapy.[29] Such disparate findings accentuate the need for randomized, prospective data in HCC to further guide clinical management in this space. Results from the currently ongoing phase III trial comparing atezo plus either lenvatinib or sorafenib *vs.* lenvatinib or sorafenib monotherapy after progression on atezo/bev (ClinicalTrials.gov ID: NCT04770896) are eagerly awaited.

In our study, slightly less than half of patients who progressed on atezo/bev transitioned to BST, while 54% continued active systemic treatment. Although there is the suggestion of improved PPS with continued treatment after PSM for confounders, given the significant baseline characteristic imbalances between the two groups – namely that patients who continued treatment were generally younger, fitter, and with lower disease burden – this result should be interpreted with caution.

We acknowledge several key limitations to this study. The retrospective nature of the dataset subjects it to the risk of selection bias and prevents drawing conclusions regarding treatment efficacy. Our findings regarding treatment outcomes and prognostic factors should be viewed as primarily hypothesis-generating for future prospective studies. With information collected from multiple institutions, there is a lack of standardization for determining treatment eligibility and frequency of patient follow-up. As with other studies drawing from retrospective datasets, missing data may have impacted some of the statistical analyses.

In our study of real-world practice patterns, we found that continuation of active treatment was significantly associated with improved PPS and should be recommended in fit patients who are able to tolerate it. While treatment selections were highly heterogenous, both single-agent TKIs and IO-based regimens appeared to remain active in the 2L setting. Mechanistically, TKIs may synergize with atezolizumab even after treatment discontinuation given the long half-life of IO agents or offer alternative molecular targets in patients who were primary refractory to IO. On the other hand, 2L IO-based regimens may be able to overcome anti-PD-L1 resistance via the addition of anti-CTLA-4 blockade. While PPS with 2L IO regimens was not significantly different compared to single-agent TKIs, the mPPS for IO-based regimens exceeded a year, adding to data supporting the use of IO after progression on atezo/bev. The therapeutic landscape in advanced HCC is rapidly evolving, simultaneously offering the promise of improved outcomes for

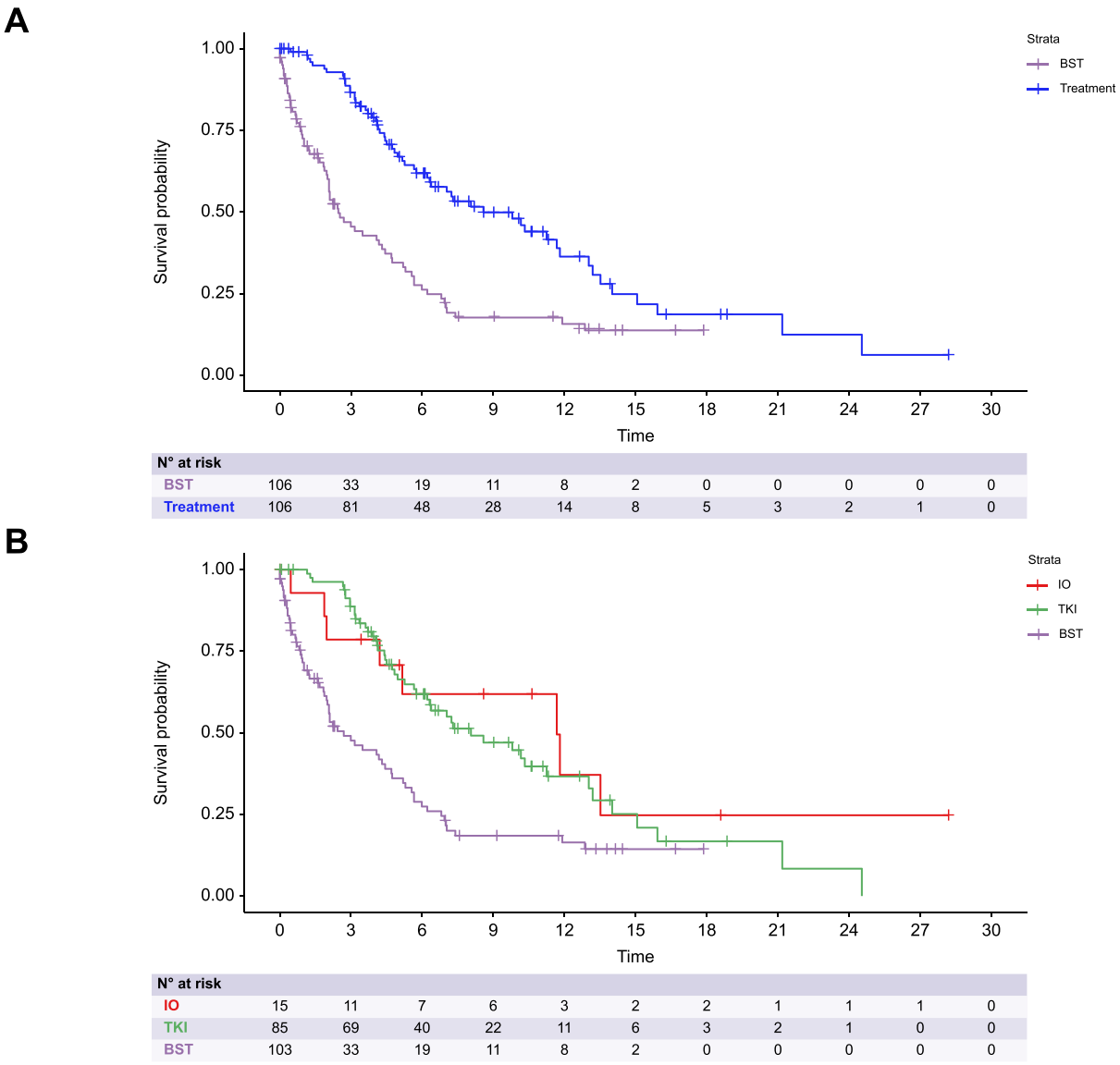

Fig. 3. Kaplan-Meier curves of PPS in a propensity score-matched population according to type of second-line treatment. Median survivals and confidence intervals were estimated using the Kaplan-Meyer method. (A) BST *vs.* active treatment; (B) BST *vs.* TKI *vs.* IO. BST, best supportive treatment; IO, immune checkpoint inhibitor; PPS, post-progression survival; TKI, tyrosine kinase inhibitor.

patients but also generating new treatment-related dilemmas for clinicians. Ultimately, prospective, randomized trials are needed to understand the optimal treatment selection and sequencing after progression on 1L treatment.

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Abbreviations

1L, first-line; 2L, second-line; BST, best supportive treatment; ECOG, Eastern Cooperative Oncology Group; IO, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; (m)PPS, (median) post-progression survival; PSM, propensity score matching; PVTT, portal vein tumor thrombosis; TKI, tyrosine kinase inhibitor.

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Conflict of interest

Celina Ang has received compensation for participating in advisory boards for Bayer and Caris Life Sciences. Lorenz Balcar has served as a speaker for Chiesi and Gilead. Ciro Celsa has received speaker fees or been on the advisory boards of AstraZeneca, MSD/Eisai, Ipsen and has received travel support from Roche. Hong Jae Chon holds consulting or advisory roles with Eisai, Roche, Bayer, ONO, MSD, BMS, Celgene, Sanofi, Servier, AstraZeneca, SillaJen, Menarini, and GreenCross Cell, and has received research grants from Roche, Dong-A ST, and Boryung Pharmaceuticals. Alessio Cortellini received grants for consultancies/advisory boards: BMS, MSD, OncoC4, IQVIA, Roche, GSK, AstraZeneca, Access Infinity, Ardelis Health and REGENERON. He also received speaker fees from AstraZeneca, EISAI, MSD, SANOFI/REGENERON and Pierre-Fabre. Antonio D'Alessio received educational support for congress attendance from Roche, and consultancy fees from Roche, Astrazeneca, and Chugai. 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Please refer to the accompanying ICMJE disclosure forms for further details.

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Data availability statement

Individual, de-identified participant raw data and data dictionary can be made available at the request of external investigators who propose to use the data in a way that has been approved by the HCC steering committee following review of a methodologically sound research proposal. Data will be made available 6 months after article publication, with no end date. Requests for de-identified data should be made to the study Chief Investigator.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101232.

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