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Real-World Study of Systemic Treatment after First-Line Atezolizumab plus Bevacizumab for Hepatocellular Carcinoma in Asia-Pacific Countries

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Keywords
Hepatocellular carcinoma · Real-world data · Asia-Pacific · Second-line treatment · Atezolizumab plus bevacizumab

Abstract
Introduction: Atezolizumab plus bevacizumab is a commonly used first-line regimen for advanced hepatocellular carcinoma (HCC) treatment owing to its superior outcomes compared to sorafenib. However, optimal subsequent treatment options for patients with HCC who progressed on first-line atezolizumab plus bevacizumab remain unclear. ***Methods:*** This multinational, multi-institutional, retrospective study included patients with HCC from 22 centers in five Asia-Pacific countries who were treated with first-line atezolizumab plus bevacizumab, which was discontinued for any reason. The endpoints included progression-free survival (PFS) and overall survival (OS) according to patient characteristics and second-line regimens. ***Results:*** Between June 2016 and May 2023, 1,141 patients were treated with first-line atezolizumab plus bevacizumab, of whom 629 (55.1%) received subsequent treatment. Sorafenib and lenvatinib were the most commonly administered second-line regimens (53.9% and 25.6%, respectively). Overall, the median PFS and OS were 2.9 and 8.0 months, respectively. Lenvatinib had longer PFS (4.0 vs. 2.3 months) and OS (8.0 vs. 6.3 months) than sorafenib. Patients treated with tyrosine kinase inhibitor (TKI) plus immune checkpoint inhibitor (ICI) (n = 50, 8.3%) showed PFS and OS of 5.4 and 12.6 months, respectively. Lower tumor burden and lenvatinib or TKI plus ICI use were associated with longer second-line PFS. Preserved liver function was associated with improved OS. ***Conclusions:*** In patients with HCC who progressed on first-line atezolizumab plus bevacizumab, sorafenib and lenvatinib were the most commonly used second-line regimens in Asia-Pacific countries, with lenvatinib resulting in longer OS than sorafenib. The second-line TKI plus ICI combination exhibited promising efficacy, suggesting the potential role of continuing ICIs beyond disease progression.

Introduction

Hepatocellular carcinoma (HCC) accounts for over 80% of primary liver cancers and is a leading cause of cancer-related death worldwide, especially in the Asia-Pacific (APAC) region [1, 2]. HCC is particularly fatal because of its delayed presentation, resistance to drug treatment, and underlying hepatic decompensation [3, 4]. The treatment landscape for HCC has greatly expanded over the last decade owing to the approval of various treatment options, especially in first-line settings. In 2018, lenvatinib, the multi-tyrosine kinase inhibitor (TKI), was approved as the first-line treatment for advanced HCC based on its non-inferiority to sorafenib, the standard of care for a decade after its approval in 2007 [5, 6]. Lenvatinib demonstrated a median overall survival (OS) of 13.6 months compared to the 12.3 months for sorafenib, as well as response rate improvement [7]. In 2020, the anti-programmed cell death ligand-1 immune checkpoint inhibitor (ICI), atezolizumab, and the anti-vascular endothelial growth factor, bevacizumab, combination demonstrated notable superior outcomes compared with sorafenib as the first line in phase III IMbrave150 trial with a median OS benefit (19.2 vs. 13.4 months) [8, 9]. In 2022, the cytotoxic T-lymphocyte-associated antigen-4 ICI, tremelimumab, in combination with the anti-programmed cell death ligand-1 inhibitor, durvalumab (Single Tremelimumab Regular Interval Durvalumab, STRIDE regimen), showed significantly improved OS compared to sorafenib (16.4 vs. 13.8 months) in the phase III HIMALAYA trial [10]. As the tremelimumab plus durvalumab regimen has not yet been reimbursed in many countries, atezolizumab plus bevacizumab (Ate/Bev) remains the main first-line treatment regimen for advanced HCC.

As all phase III trials that led to second- or later-line treatment option approval for advanced HCC, such as regorafenib [11], cabozantinib [12], and ramucirumab [13], have been conducted in patients who progressed from first-line sorafenib treatment, there are currently no high-level evidence-based second- or later-line treatment options for patients who progressed from the current first-line treatment regimen, especially the most commonly used regimen, Ate/Bev. Moreover, randomized phase III studies comparing second-line options after the current first-line therapies have not yet been conducted. Hence, a comprehensive study is needed to compare the currently available second-line treatment options after Ate/Bev.

In this large-scale, multinational real-world study, we aimed to compare the efficacy of different systemic second-line treatment options in patients with HCC who progressed on first-line Ate/Bev in the APAC region. Moreover, we investigated the clinical factors that could predict survival benefits in patients receiving second-line treatment following Ate/Bev treatment.

Methods

Patients

A retrospective cohort analysis was performed at 22 tertiary hospitals in five APAC countries (South Korea, Hong Kong, Taiwan, Thailand, and Singapore). Using electronic medical records, we identified patients with histologically or clinically confirmed HCC according to international guidelines [14, 15]. Furthermore, these patients were treated with palliative first-line Ate/Bev, which was either discontinued or concluded for any reason. The following data were retrospectively collected: age at the beginning of treatment, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), etiology, previous local therapy (surgery, radiotherapy, radiofrequency ablation, transarterial chemoembolization, or transarterial radioembolization) history, Child-Pugh scale, Barcelona Clinic Liver Cancer (BCLC) stage, major vascular invasion of tumor, esophageal varix status, metastatic sites, tumor marker, laboratory results at the beginning of first-line or second-line treatment, second-line or third-line regimen (if available), toxicity, and treatment outcomes (response and survival). The study was reviewed and approved by the Protocol Review Committee of the Korea Cancer Study Group (KCSG HB22-21) and the institutional review boards and ethics committees of each institution. The need for informed consent was waived by the KCSG Review Committee and the institutional review boards of each institution owing to the retrospective nature of the study.

Outcomes and Statistical Analyses

The primary endpoint of this study was to compare progression-free survival (PFS) and OS achieved using different second-line treatment regimens. Other endpoints included reasons for Ate/Bev treatment discontinuation, the relationship between first- and second-line PFS, and clinical patient characteristics that could affect second-line survival. Treatment response and progression were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Descriptive statistics for categorical variables such as baseline characteristics were presented as counts with percentages and compared using the χ^2 test or Fisher's exact test. The Kaplan-Meier method was used to estimate survival, and the log-rank test was applied to determine the difference in survival between the groups. The Cox proportional hazards model was used in the univariable and multivariable analyses to assess the significant prognostic factors associated with OS and PFS, with the hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with a level of significance of $p < 0.1$ in the univariable analyses were only included in multivariable analyses. The proportional hazard assumption was evaluated using a global test based on the Schoenfeld residuals. Patient-level correlation between first-line and second-line PFS with each treatment regimen was assessed using Spearman's rank correlation coefficient. We conducted propensity score matching (PSM) to compare PFS and OS in patients who received sorafenib or lenvatinib following Ate/Bev. Propensity scores were estimated in each imputed dataset using a multivariable logistic regression model that included age, sex, ECOG PS, AFP level, presence of extrahepatic spread, prior local therapy, Child-Pugh score, and mALBI grade. PSM was performed using 1:1 nearest-neighbor matching without replacement, with a caliper width set to 0.2 of the standard deviation of the propensity score. To assess covariate balance, we evaluated pre-match imbalances and post-match balance using standardized mean differences. Statistical testing of patient characteristics between treatment groups included χ^2 tests for categorical variables in the pre-match comparison, and McNemar tests and stratified log-rank tests for categorical variables and time-dependent outcomes, respectively, in the post-match analysis. Two-sided $p < 0.05$ were considered statistically significant. All statistical analyses and graphing were performed using the R statistical software package R 4.3.1 (R project; the R Foundation for Statistical Computing, Vienna, Austria) or SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Patients and Reasons for First-Line Ate/Bev Discontinuation

Between June 2016 and May 2023, 1,141 patients from five APAC countries with HCC treated with first-line Ate/Bev that had discontinued treatment for any reason were analyzed. The median follow-up duration was 19.9 months (95% CI: 18.4–21.9). A total of 629 patients (55.1%) underwent subsequent treatments (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000540969). The main reasons for the discontinuation of first-line Ate/Bev included disease progression (76.8%), toxicity (9.8%), and transfer to another hospital or loss to follow-up (7.6%). Twenty-six patients (2.3%) finished 2-year treatment with Ate/Bev without progression (online suppl. Fig. S2). The baseline

Table 1. Baseline patient characteristics

	Total (n = 1,141)	No more Tx (n = 512)	Second-line Tx (n = 629)	p value
Median age (IQR)	62 (54–70)	63 (55–72)	60 (53–68)	–
Age	–	–	–	0.0007
<65 years	682 (59.8%)	278 (54.3%)	404 (64.2%)	–
≥65 years	459 (40.2%)	234 (45.7%)	225 (35.8%)	–
Sex, n (%)	–	–	–	0.5167
Male	956 (83.8%)	433 (84.6%)	523 (83.1%)	–
Female	185 (16.2%)	79 (15.4%)	106 (16.9%)	–
ECOG PS	–	–	–	<0.0001
0	425 (37.2%)	158 (30.9%)	267 (42.4%)	–
1	661 (57.9%)	318 (62.1%)	343 (54.5%)	–
2	44 (3.9%)	29 (5.7%)	15 (2.4%)	–
3–4	11 (1.0%)	7 (1.4%)	4 (0.7%)	–
Previous treatment	–	–	–	–
Surgery	359 (31.5%)	124 (24.2%)	235 (37.4%)	<0.0001
RFA	146 (12.8%)	61 (11.9%)	85 (13.5%)	0.4212
TACE or TARE	581 (50.9%)	229 (44.7%)	352 (56.0%)	0.0002
RTx to liver	240 (21.0%)	103 (20.1%)	137 (21.8%)	0.0269
RTx to other site	69 (6.0%)	21 (4.1%)	48 (7.6%)	
Macrovascular invasion (MVI)	–	–	–	<0.0001
Absent	667 (58.5%)	243 (47.5%)	424 (67.4%)	–
Present	473 (41.4%)	269 (52.5%)	204 (32.4%)	–
Vp4 present	217 (19.0%)	125 (24.4%)	92 (14.6%)	–
Unknown	1 (0.1%)	0 (0%)	1 (0.2%)	–
Esophageal varix	–	–	–	0.0017
Absent	507 (44.4%)	198 (38.7%)	309 (49.1%)	–
Present	287 (25.2%)	145 (28.3%)	142 (22.6%)	–
Unknown	347 (30.4%)	169 (33.0%)	178 (28.3%)	–
Maximum intrahepatic tumor diameter, cm	–	–	–	<0.0001
Median (IQR)	6.1 (3.0, 11.0)	7.4 (3.4, 13.0)	5.4 (2.8, 9.9)	–
Number of intrahepatic tumors	–	–	–	0.0168
None	156 (13.7%)	54 (10.5%)	102 (16.2%)	–
Single	231 (20.2%)	112 (21.9%)	119 (18.9%)	–
Multiple	754 (66.1%)	346 (67.6%)	408 (64.9%)	–
Extrahepatic spread	–	–	–	0.0313
Absent	377 (33.0%)	186 (36.3%)	191 (30.4%)	–
Present	764 (67.0%)	326 (63.7%)	438 (69.6%)	–
Etiology				
HBV	784 (68.7%)	332 (64.8%)	452 (71.9%)	0.0010
HCV	76 (6.7%)	36 (7.0%)	40 (6.4%)	0.6507
Alcohol	159 (13.9%)	83 (16.2%)	76 (12.1%)	0.0452
MASLD	84 (7.4%)	48 (9.4%)	36 (5.7%)	0.0188
Others	79 (6.9%)	35 (6.8%)	44 (7.0%)	0.9160
Child-Pugh score	–	–	–	<0.0001
5	663 (58.1%)	239 (46.7%)	424 (67.4%)	–
6	296 (25.9%)	159 (31.1%)	137 (21.8%)	–
7	105 (9.2%)	62 (12.1%)	43 (6.8%)	–
8–10	54 (4.7%)	46 (9.0%)	8 (1.3%)	–
Unknown	23 (2.0%)	6 (1.2%)	17 (2.7%)	–

Table 1 (continued)

	Total (n = 1,141)	No more Tx (n = 512)	Second-line Tx (n = 629)	p value
BCLC stage	–	–	–	<0.0001
A	6 (0.5%)	2 (0.4%)	4 (0.6%)	–
B	151 (13.2%)	52 (10.2%)	99 (15.7%)	–
C	925 (81.1%)	416 (81.3%)	509 (80.9%)	–
D	38 (3.3%)	38 (7.4%)	0 (0%)	–
Unknown	21 (1.8%)	4 (0.8%)	17 (2.7%)	–

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; RTx, radiotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; BCLC, Barcelona Clinical Liver Cancer.

characteristics of the patients who did not receive subsequent treatment (n = 512, no more treatment group) and those who were treated with second-line systemic therapy (n = 629, subsequent treatment group) are listed in Table 1. Overall, patients who received subsequent systemic treatment had a better ECOG PS (0, 42.4 vs. 30.9%, $p < 0.0001$), better liver function in terms of Child-Pugh score (score of 5, 67.4 vs. 46.7%, $p < 0.0001$), and less advanced BCLC stage (stage B, 15.7 vs. 10.2%, $p < 0.0001$) than those in the no more treatment group. None of the patients with BCLC stage D disease (n = 38, 7.4%) received subsequent treatment. A history of local therapy was common among the patients who received subsequent treatment (73.5 vs. 59.6%, $p < 0.0001$). B viral etiology was more common in the subsequent treatment group (71.9 vs. 64.8%, p = 0.001), whereas nonviral etiologies (alcohol or metabolic dysfunction-associated steatotic liver disease) were less common than in the no more treatment group. Among patients who did not receive second-line systemic treatment after Ate/Bev (n = 512), patients who finished 2-year treatment (n = 24, 4.7%) showed durable OS (median OS not reached), and patients who discontinued Ate/Bev due to toxicity (n = 93, 18.2%) showed a median OS of 12.1 (95% CI, 7.8–18.8) months. However, patients who progressed to Ate/Bev and could not receive second-line treatment exhibited a median OS of only 5.2 (95% CI, 4.2–6.1) months (online suppl. Fig. S3A). The OS was longer in patients who received second-line treatment (median OS 14.7 vs. 7.3 months; HR, 0.64; 95% CI, 0.55–0.75; $p < 0.0001$) (online suppl. Fig. S3B).

Subsequent Treatment Sequences and Outcomes

Among the 629 patients who received second-line treatment, 605 were available for survival analyses after excluding patients whose follow-up duration was less than 2 weeks (n = 24). With the median follow-up duration after second-line initiation of 12.3 months (95% CI, 10.8–14.2), overall median second-line PFS and OS was 3.0 months (95% CI, 2.7–3.4) and 8.0 months (95% CI, 7.2–9.3), respectively (online suppl. Fig. S4). The real-world treatment sequence for APAC patients with HCC after Ate/Bev discontinuation is shown in Figure 1. Sorafenib was the most commonly used second-line regimen (n = 339, 53.9%), followed by lenvatinib (n = 161, 25.6%), TKI plus ICI (n = 50, 7.9%), regorafenib (n = 37, 5.9%), and cabozantinib (n = 12, 1.9%) (online suppl. Fig. S5). Among the patients who received second-line treatment, 283 (46.3% of 611 patients who started second-line treatment, excluding 18 patients who were on second-line treatment at the data cutoff) received third-line treatment. The most commonly used third-line treatment regimen was regorafenib (n = 100, 35.3%), and the majority of patients who received third-line regorafenib experienced treatment failure. Sorafenib was the most commonly used regimen after second-line lenvatinib treatment failure.

Clinical patient characteristics according to the second-line regimen at the time of second-line treatment initiation are summarized in Table 2. There was a statistically significant difference between the different second-line treatment regimens in terms of PFS ($p < 0.0001$) and OS (p = 0.0003) (Fig. 2). In particular, patients treated with sorafenib (n = 324) in second-line therapy achieved median PFS and OS of 2.3 months (95% CI, 2.0–2.6) and 6.3 months (95% CI, 5.3–7.8), respectively, where lenvatinib (n = 154) as second-line after Ate/Bev demonstrated median PFS and OS of 4.0 months (95% CI, 3.5–4.9) and 8.0 months (95% CI, 7.0–10.9), respectively. Patients who received lenvatinib had a significantly longer PFS and OS than those treated with sorafenib in the second-line setting (HR 0.53, 95%

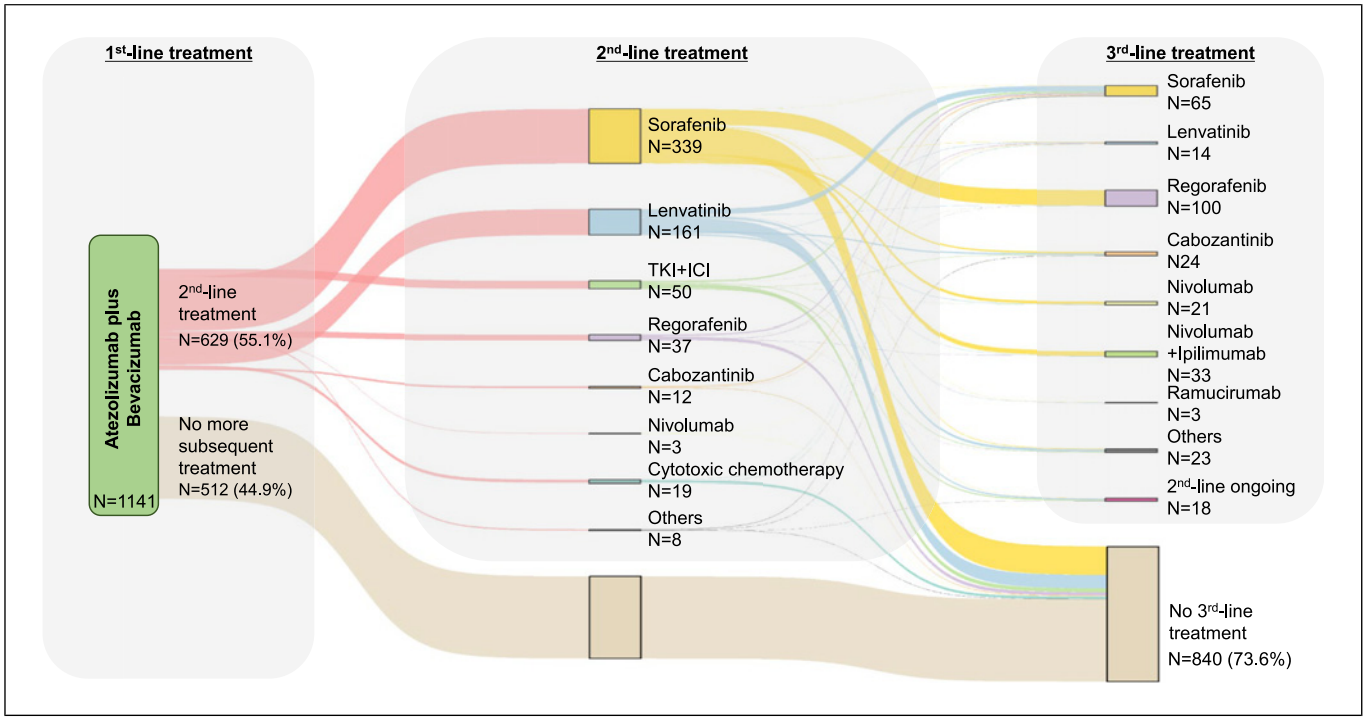


Fig. 1. Subsequent treatment distribution after first-line Ate/Bev for APAC patients with HCC (n = 1,141).

CI: 0.43–0.67, $p < 0.0001$ for PFS; HR 0.75, 95% CI: 0.59–0.96, $p = 0.0230$ for OS) (online suppl. Fig. S6, S7). Second-line lenvatinib showed significantly longer PFS compared to sorafenib even after PSM (online suppl. Table S1; Fig. S8). Compared to sorafenib, regorafenib and cabozantinib exhibited better PFS (HR 0.64, 95% CI: 0.43–0.97 for regorafenib; HR 0.47, 95% CI: 0.24–0.91 for cabozantinib), but no statistical benefit in terms of OS (HR 0.64, 95% CI: 0.36–1.12 for regorafenib; HR 0.62, 95% CI: 0.31–1.26 for cabozantinib), which was likely due to the small number of patients. Various TKI plus ICI regimens were used as second-line treatment following Ate/Bev (n = 50) and showed durable survival in terms of median PFS (5.4 months; 95% CI, 3.0–8.8; HR 0.32, 95% CI: 0.22–0.47 compared with sorafenib) and OS (12.6 months; 95% CI, 9.8–not reached; HR 0.41, 95% CI: 0.26–0.64 compared with sorafenib). Second-line efficacy data, including response rates, are summarized in online supplementary Table S2.

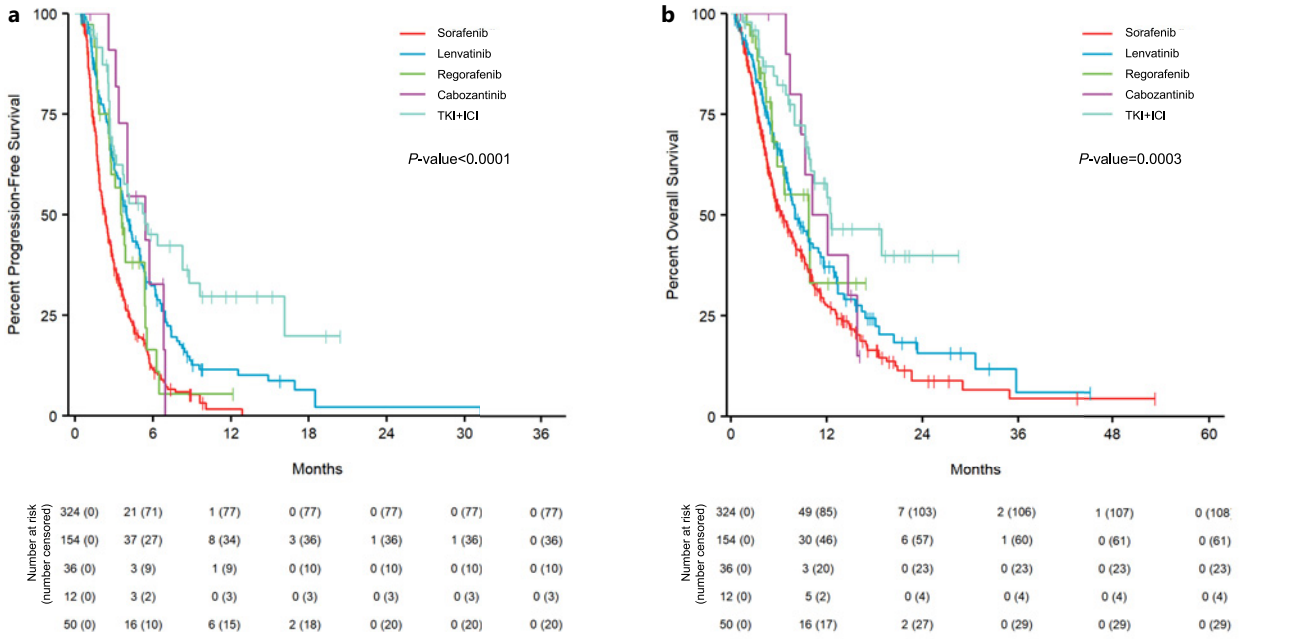
To determine whether overcoming early or de novo resistance to atezolizumab and bevacizumab by a specific second-line regimen is possible, we further analyzed the correlation between first-line PFS with atezolizumab plus bevacizumab (PFS1) and the second-line PFS with each treatment regimen (PFS2) (Fig. 3a). There was an overall positive correlation between PFS1 and PFS2 ($r = 0.204$, $p < 0.0001$), implying that patients who benefited from first-line Ate/Bev also benefited from second-line treatment. Notably, when TKI monotherapy (lenvatinib, sorafenib, regorafenib, or cabozantinib) showed a similar positive correlation between PFS1 and PFS2 ($r = 0.214$, $p < 0.0001$, Fig. 3b), PFS2 in the TKI plus ICI group did not correlate with PFS1 (correlation $r = -0.0237$, $p = 0.8751$, Fig. 3c).

Subgroup analyses were performed for patients who received second-line therapy (n = 605) (Fig. 4). As expected, patients with good performance (lower ECOG PS) and lower alpha-fetoprotein (AFP) levels (<400 ng/mL) showed improved survival. In addition, patients with preserved liver function at the initiation of second-line treatment, in terms of lower Child-Pugh scores and modified albumin-bilirubin (mALBI) grades, had better survival than those with diminished liver function, which are known favorable prognostic factors for HCC patients. In addition, patients with macrovascular invasion (MVI), esophageal varix, and extrahepatic spread exhibited low survival in terms of PFS and/or OS (online suppl. Fig. S9–11). Finally, we conducted multivariable analyses using Cox proportional hazard regression, considering

Table 2. Patient characteristics as per second-line regimens

	Total (n = 605)	Sorafenib (n = 324)	Lenvatinib (n = 154)	Regorafenib (n = 36)	Cabozantinib (n = 12)	TKI+ICI (n = 50)
Median age (IQR)	60 (53–68)	61 (54–69)	61 (52–70)	56 (50–62)	61 (49–63)	62 (54–67)
Age						
<65 years	390 (64.5%)	202 (62.3%)	94 (61.0%)	29 (80.6%)	10 (83.3%)	31 (62.0%)
≥65 years	215 (35.5%)	122 (37.7%)	60 (39.0%)	7 (19.4%)	2 (16.7%)	19 (38.0%)
Sex, n (%)						
Male	502 (83.1%)	264 (81.5%)	128 (83.1%)	28 (77.8%)	11 (91.7%)	44 (88.0%)
Female	102 (16.9%)	60 (18.5%)	26 (16.9%)	8 (22.2%)	1 (8.3%)	6 (12.0%)
ECOG PS						
0	258 (42.6%)	124 (38.3%)	77 (50.0%)	15 (41.7%)	2 (16.7%)	27 (54.0%)
1	330 (54.5%)	192 (59.3%)	71 (46.1%)	21 (58.3%)	10 (83.3%)	20 (40.0%)
2	15 (2.5%)	7 (2.2%)	6 (3.9%)	0 (0%)	0 (0%)	2 (4.0%)
3–4	2 (0.3%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)
Previous treatment						
Surgery	230 (38.0%)	129 (39.8%)	63 (40.9%)	14 (38.9%)	4 (33.3%)	14 (28.0%)
RFA	82 (13.6%)	48 (14.8%)	22 (14.3%)	2 (5.6%)	1 (8.3%)	4 (8.0%)
TACE/TARE	336 (55.5%)	186 (57.4%)	77 (50.0%)	27 (75.0%)	7 (58.3%)	24 (48.0%)
RTx to liver	130 (21.5%)	75 (23.1%)	29 (18.8%)	8 (22.2%)	4 (33.3%)	6 (12.0%)
RTx to other site	46 (7.6%)	28 (8.6%)	7 (4.5%)	3 (8.3%)	0 (0%)	6 (12.0%)
Macrovascular invasion						
Absent	316 (52.2%)	152 (46.9%)	102 (66.2%)	7 (19.4%)	8 (66.7%)	34 (68.0%)
Present	162 (26.8%)	90 (27.8%)	42 (27.3%)	5 (13.9%)	2 (16.7%)	12 (24.0%)
Vp4 present	74 (12.2%)	40 (12.3%)	15 (9.7%)	3 (8.3%)	1 (8.3%)	7 (14.0%)
Unknown	127 (21.0%)	82 (25.3%)	10 (6.5%)	24 (66.7%)	2 (16.7%)	4 (8.0%)
Extrahepatic spread						
Absent	125 (20.7%)	53 (16.4%)	41 (26.6%)	1 (2.8%)	2 (16.8%)	17 (34.0%)
Present	360 (59.5%)	193 (59.6%)	106 (68.8%)	11 (30.6%)	8 (66.7%)	29 (58.0%)
Unknown	120 (19.8%)	78 (24.1%)	7 (4.5%)	24 (66.7%)	2 (16.7%)	4 (8.0%)
Etiology						
HBV	435 (71.9%)	225 (69.4%)	109 (70.8%)	29 (80.6%)	8 (66.7%)	39 (78.0%)
HCV	38 (6.3%)	19 (5.9%)	8 (5.2%)	4 (11.1%)	1 (8.3%)	3 (6.0%)
Alcohol	71 (11.7%)	46 (14.2%)	18 (11.7%)	0 (0%)	1 (8.3%)	4 (8.0%)
MASLD	36 (6.0%)	15 (4.6%)	16 (10.4%)	1 (2.8%)	0 (0%)	4 (8.0%)
Child-Pugh score						
5	316 (52.2%)	146 (45.1%)	102 (66.2%)	23 (63.9%)	4 (33.3%)	28 (56.0%)
6	166 (27.4%)	89 (27.5%)	33 (21.4%)	11 (30.6%)	7 (58.3%)	16 (32.0%)
7	71 (11.7%)	54 (16.7%)	10 (6.5%)	2 (5.6%)	1 (8.3%)	1 (2.0%)
8–10	29 (4.8%)	26 (8.0%)	3 (1.9%)	0 (0%)	0 (0%)	0 (0%)
Unknown	23 (3.8%)	9 (2.8%)	6 (3.9%)	0 (0%)	0 (0%)	5 (10.0%)
BCLC stage						
1	5 (0.8%)	2 (0.6%)	1 (0.6%)	0 (0%)	0 (0%)	2 (4.0%)
2	63 (10.4%)	28 (8.6%)	22 (14.3%)	1 (2.8%)	1 (8.3%)	9 (18.0%)
3	448 (74.0%)	247 (76.2%)	125 (80.5%)	12 (33.3%)	9 (75.0%)	34 (68.0%)
4	3 (0.5%)	2 (0.6%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Unknown	86 (14.2%)	45 (13.9%)	6 (3.9%)	23 (63.9%)	2 (16.7%)	5 (10.0%)
AFP						
≤400 ng/mL	276 (45.6%)	139 (42.9%)	80 (51.9%)	8 (22.2%)	2 (16.7%)	30 (60.0%)
>400 ng/mL	241 (39.8%)	133 (41.0%)	68 (44.2%)	5 (13.9%)	7 (58.3%)	20 (40.0%)
Unknown	88 (14.5%)	52 (16.0%)	6 (3.9%)	23 (63.9%)	3 (25.0%)	0 (0%)

TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; RTx, radiotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; BCLC, Barcelona Clinical Liver Cancer; AFP, α-fetoprotein.



Treatment Group	n	# of events	Median PFS (95% CI)
Sorafenib	324	247	2.3 (2.0 – 2.6)
Lenvatinib	154	118	4.0 (3.5 – 4.9)
Regorafenib	36	26	3.6 (2.7 – 5.4)
Cabozantinib	12	9	5.4 (3.1 – 6.8)
TKI + ICI	50	30	5.4 (3.0 – 8.8)

Treatment Group	n	# of events	Median OS (95% CI)
Sorafenib	324	216	6.3 (5.3 – 7.8)
Lenvatinib	154	93	8.0 (7.0 – 10.9)
Regorafenib	36	13	9.7 (5.2 – NR)
Cabozantinib	12	8	11.2 (6.9 – 15.8)
TKI + ICI	50	21	12.6 (9.8 – NR)

Fig. 2. PFS and OS of patients who received second-line therapy. Kaplan-Meier survival curves with PFS (**a**) and OS (**b**) in months stratified by second-line treatment regimens (n = 605). TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

variables that significantly affected second-line PFS and OS after atezolizumab and bevacizumab administration in the univariate analysis (Table 3). Notably, higher AFP levels (AFP ≥400 ng/mL) and lenvatinib or TKI plus ICI use (compared with sorafenib) were the only variables that significantly affected PFS after considering performance status, MVI, extrahepatic spread, esophageal varix, Child-Pugh score, and mALBI grade. Regarding OS, the ECOG PS, Child-Pugh score, mALBI grade, and TKI plus ICI use (compared with sorafenib) were significantly affected.

Discussion

In this study, we investigated a large-scale cohort of patients with HCC from APAC countries treated with first-line Ate/Bev and compared the subsequent treatment efficacy and prognostic factors. To our knowledge, this is the first large multinational cohort study to report the treatment pattern of patients treated with Ate/Bev in APAC countries, which comprise the largest number of patients treated with first-line Ate/Bev to date.

Our data revealed that approximately half (55%) of the patients with HCC in APAC countries receive second-line treatment after Ate/Bev discontinuation, which is consistent with previous reports [16]. Compared with the use of second-line treatment of 33% at the time when the REFLECT trial was conducted, our study showed a trend of increasing use of second-line treatment [17]. Approximately half (46%) of the patients treated with second-line therapy also received third-line treatment. Overall, 26.4% of patients received third-line treatment after Ate/Bev treatment.

The OS of the Ate/Bev cohort appeared to be shorter (14.7 months for patients who received second-line treatment) than that of the IMbrave 150 data (OS of 19.2 months) [9] but comparable to previous reports

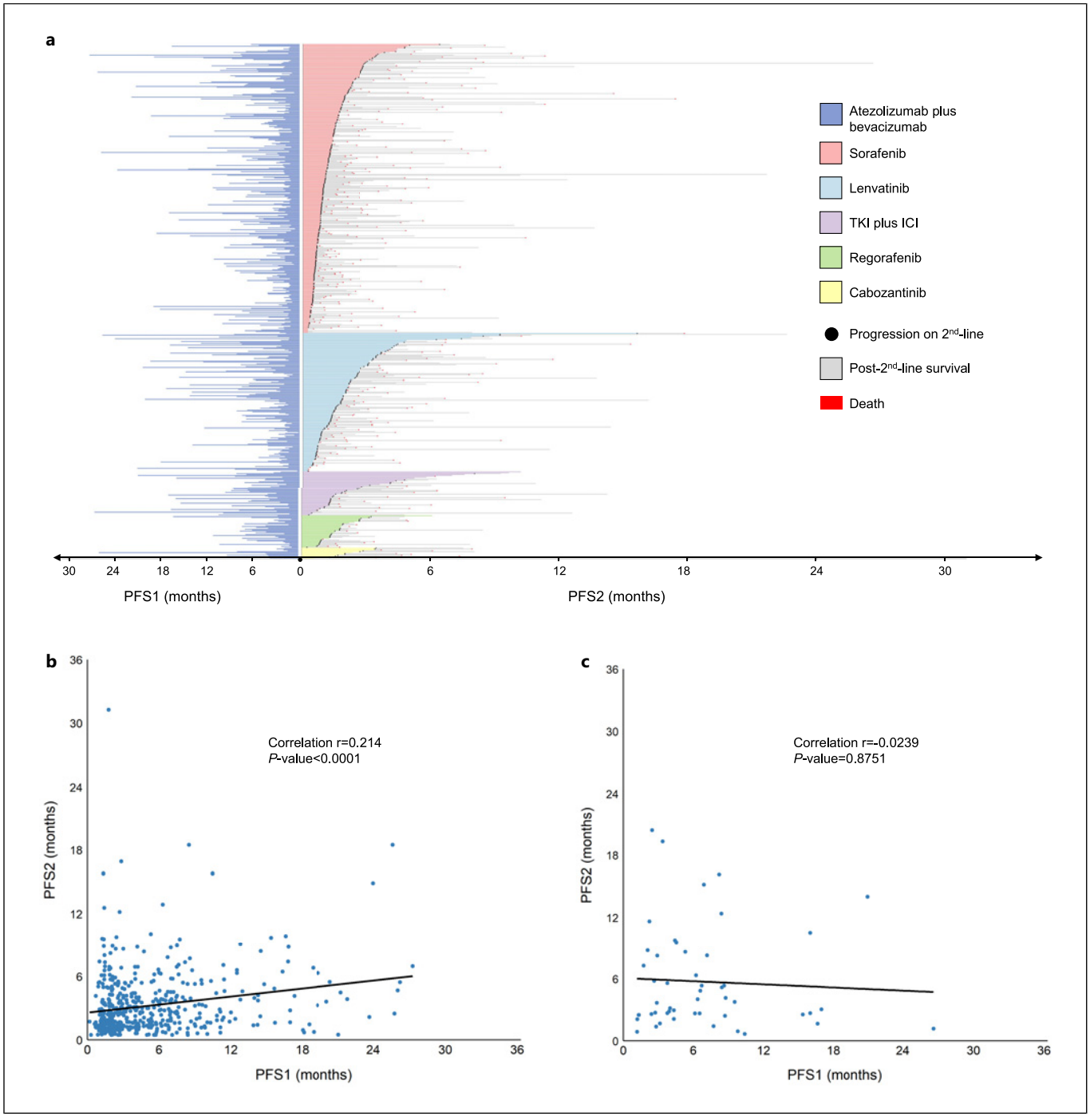
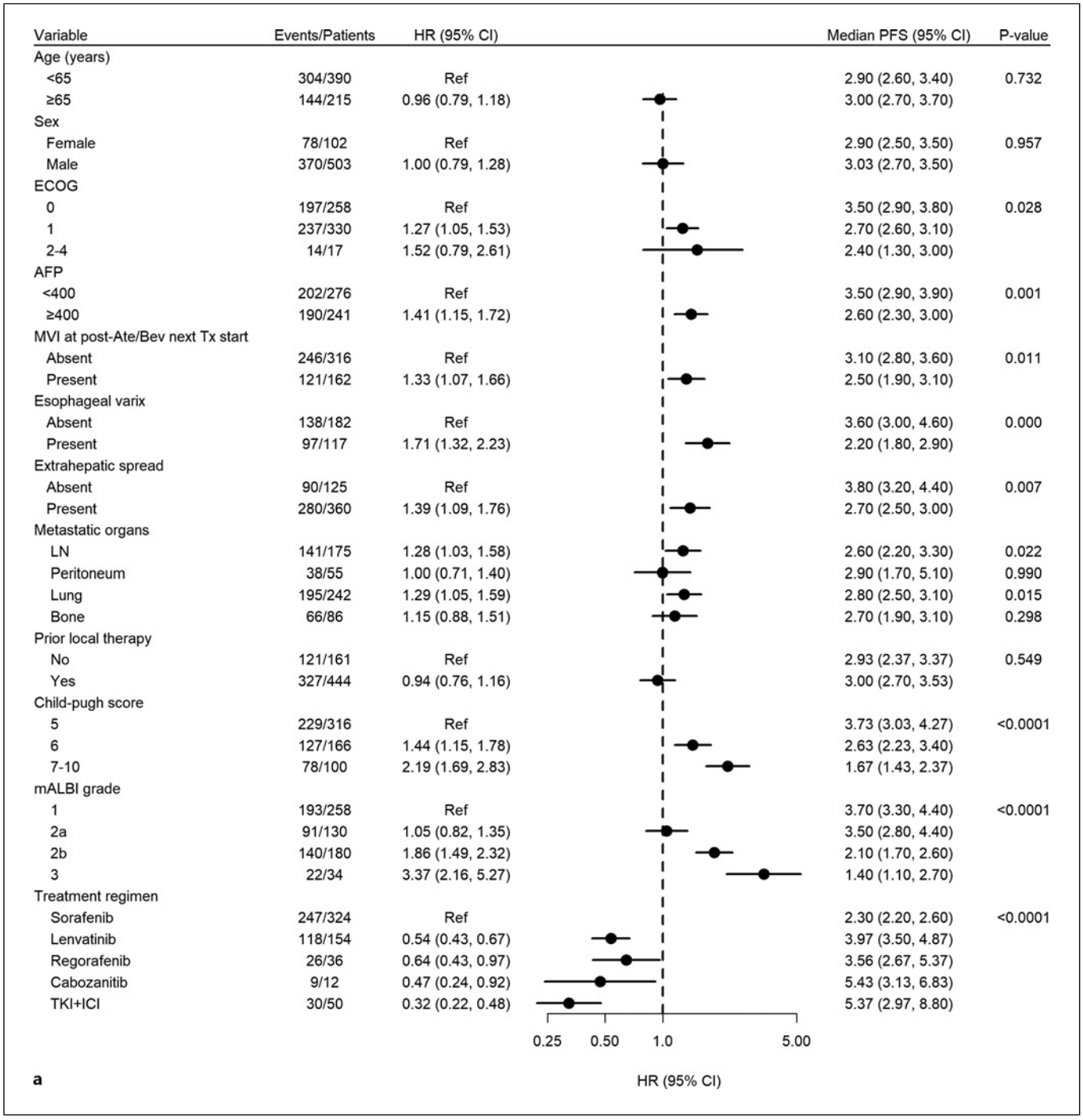


Fig. 3. Correlation between PFS of Ate/Bev and second-line treatment regimens. **a** Swimmer's plot showing the PFS1 and PFS2. **b**, **c** Correlation between PFS1 and PFS2 for patients treated with second-line TKIs (lenvatinib, sorafenib, regorafenib, or cabozantinib) (**b**, $n = 526$) and TKI plus ICIs (**c**, $n = 50$). TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; PFS, progression-free survival; PFS1, first-line PFS of atezolizumab plus bevacizumab; PFS2, second-line PFS of each indicated treatment regimen.



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(15.7 months) [16]. This is attributable to the fact that we excluded patients who were currently receiving Ate/Bev; thus, the outcomes were underestimated by excluding durable responders to Ate/Bev. In addition, patients beyond the IMbrave 150 inclusion criteria were treated with Ate/Bev in the real world, such as those with an ECOG PS of 2–4 (4.9%) and a Child-Pugh score of B or C (13.9%). In our analyses, patients who did not receive second-line treatment after disease progression to Ate/Bev showed a median OS of 5.2 months (online suppl.

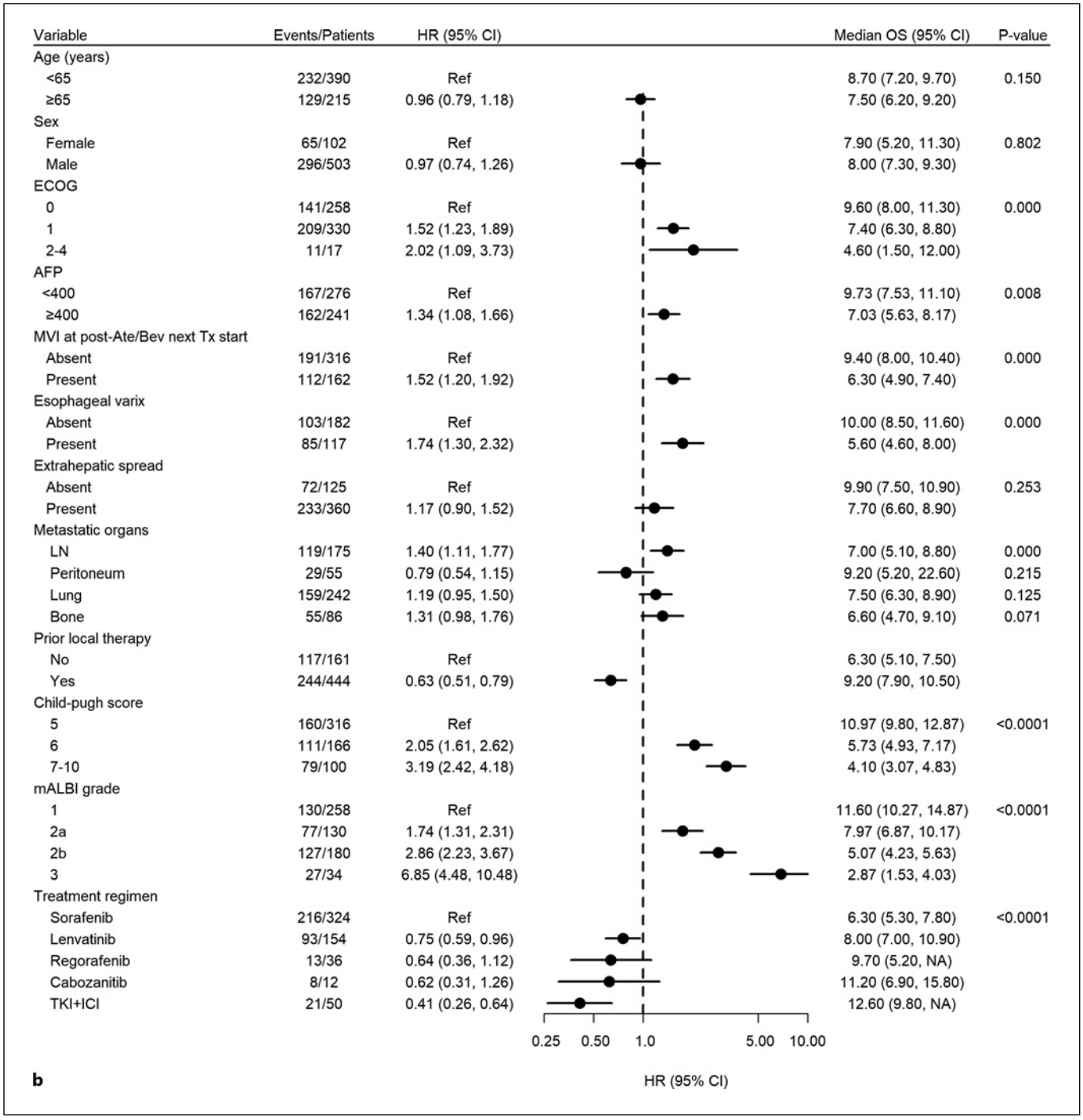

Fig. 4. Subgroup analyses for second-line PFS and OS. Forest plot of subgroup analysis of PFS (**a**) and OS (**b**) for patients receiving second-line regimens ($n = 605$) according to baseline demographic and disease characteristics after Ate/Bev Tx initiation. HRs for the patient subgroups were obtained from unstratified analyses using the Cox proportional hazards model. The CIs for the subgroup analyses were not adjusted for multiple comparisons. Ref, reference; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; MVI, macrovascular invasion; LN, lymph node; mALBI, modified albumin-bilirubin; TKI + ICI, tyrosine kinase inhibitor plus immune checkpoint inhibitor; PFS, progression-free survival; OS, overall survival; Ate/Bev, atezolizumab plus bevacizumab; Tx, next treatment; HRs, hazard ratios; CIs, confidence intervals.

Table 3. Multivariable analysis using Cox proportional hazard regression for second-line PFS and OS

Variable	PFS		OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
ECOG PS				
0	Reference	–	Reference	–
1	1.22 (0.90–1.66)	0.1914	1.71 (1.20–2.42)	0.0026
2–4	2.55 (0.98–6.64)	0.0544	2.06 (0.71–5.98)	0.1857
AFP				
<400 ng/mL	Reference	–	Reference	–
≥400 ng/mL	1.34 (1.01–1.77)	0.0432	1.32 (0.96–1.81)	0.0838
MVI at post-atezolizumab/bevacizumab next treatment start				
Absent	Reference	–	Reference	–
Present	0.89 (0.66–1.22)	0.4583	0.96 (0.60–1.22)	0.4026
Extrahepatic spread				
Absent	Reference	–	Reference	–
Present	1.27 (0.02–1.76)	0.1426	1.18 (0.82–1.70)	0.3655
Esophageal varix				
Absent	Reference	–	Reference	–
Present	1.33 (0.97–1.84)	0.0794	0.96 (0.69–1.37)	0.8318
Child-Pugh score				
5	Reference	–	Reference	–
6	1.20 (0.81–1.76)	0.3614	1.74 (1.11–2.73)	0.0152
7–10	1.54 (0.87–2.72)	0.1362	2.47 (1.30–4.71)	0.0058
mALBI grade				
1	Reference	–	Reference	–
2a	0.95 (0.66–1.35)	0.7615	1.79 (1.19–2.70)	0.0050
2b	1.09 (0.70–1.70)	0.6961	1.50 (0.89–2.55)	0.1301
3	1.33 (0.59–3.02)	0.4928	2.32 (0.86–5.58)	0.0613
Treatment regimen				
Sorafenib	Reference	–	Reference	–
Lenvatinib	0.63 (0.45–0.89)	0.0076	1.04 (0.72–1.50)	0.8491
Regorafenib	1.68 (0.86–3.29)	0.1306	1.38 (0.58–3.28)	0.4606
Cabozantinib	0.45 (0.14–1.43)	0.1764	0.59 (0.18–1.92)	0.3839
TKI+ICI	0.37 (0.22–0.62)	0.0001	0.41 (0.22–0.75)	0.0038
Others	0.76 (0.39–1.53)	0.4638	0.63 (0.26–1.58)	0.3228

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; MVI, macrovascular invasion; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; mALBI, modified albumin-bilirubin.

Fig. S3), highlighting the importance of subsequent treatment.

Among second-line treatment options, sorafenib (53.9%) was the most commonly used regimen after Ate/Bev treatment, probably because of the lack of reimbursement for other treatment regimens in many countries. Another first-line approved TKI, lenvatinib, was the next most commonly used regimen (25.6%) and showed better survival than second-line sorafenib (HR: PFS, 0.53, and OS, 0.75). Even after multivariable analysis, lenvatinib use was a significant factor that led to improved PFS after Ate/Bev treatment. The superior outcome of lenvatinib compared with sorafenib after first-line Ate/Bev treatment was suggested by a previous Asian multicenter retrospective study that demonstrated a significant PFS benefit for lenvatinib compared with sorafenib but not for OS, likely due to the small sample size [18]. Other approved TKIs for later lines of HCC, regorafenib and cabozantinib, also exhibited better PFS than sorafenib. Recently, a single-arm phase II study reported an OS of 14.3 months for second-line cabozantinib after Ate/Bev treatment [19]. The ongoing REGONEXT trial evaluates the survival outcomes

of regorafenib use in patients who have progressed from Ate/Bev [20]. These results support the need for randomized prospective trials that can lead to the reimbursement of TKIs other than sorafenib as second-line treatments after Ate/Bev treatment. Recently, a global retrospective study comprising 464 patients treated with first-line atezolizumab and bevacizumab showed statistically significant superior OS of second-line lenvatinib over sorafenib (HR, 0.50; 95% CI, 0.27–0.92) but not with other systemic treatments (cabozantinib HR, 1.34, and 95% CI, 0.55–3.26; other therapies HR, 0.54, and 95% CI, 0.28–1.03) [16]. This may be due to the relatively small number of patients in the other TKI-treated groups, showing the advantage of our study with the largest number of patients treated with Ate/Bev.

The combination of TKI and ICI as second-line treatment showed the most durable survival (PFS of 5.4 months, OS of 12.6 months from second-line initiation, and OS of 22.6 months from Ate/Bev initiation), even after multivariable analyses, suggesting a potential role for continuing ICIs beyond disease progression. However, various regimens were included, and as most patients were treated in clinical trial settings, caution was advised when interpreting these results. When we compared PFS1 and PFS2, the PFS2 of TKI monotherapy was positively correlated with PFS1, but the PFS2 of TKI plus ICI was not correlated with PFS1 (Fig. 3). This interesting result may be because (1) patients with short PFS1 on Ate/Bev may benefit from TKI addition after progression, and (2) patients who already showed long-term response to first-line Ate/Bev treatment may not benefit from continuing ICI beyond disease progression. These hypotheses should be tested in future studies. Currently, ongoing trials of IMbrave 251 (NCT04770896) and ACCRU-GI-2008 (NCT05168163) evaluate the continuum of atezolizumab in combination with TKIs (lenvatinib or sorafenib for IMbrave 251 and cabozantinib or lenvatinib for ACCRU-GI-2008) compared to TKI alone, after progression from Ate/Bev treatment. These results provide insights into future second-line treatments after atezolizumab and bevacizumab treatment.

Subgroup analyses showed that previously known prognostic factors for patients with HCC, including preserved liver function, absence of MVI, and lower tumor burden in terms of lower AFP levels or absence of extrahepatic spread, led to longer survival in patients with HCC receiving second-line treatments. The importance of hepatic reserve function is well known, especially for second-line regimens following Ate/Bev treatment [21, 22]. In our study, preserved liver function in terms of Child-Pugh score and mALBI grade were significantly associated with OS after multivariable analyses. Even after considering tumor burden or hepatic reserve functions in multivariable analyses, lenvatinib or TKI plus ICI usage, along with lower AFP levels, was significantly associated with longer PFS after Ate/Bev treatment.

This study had some limitations owing to its retrospective nature. We could not exclude selection bias; some patients had missing data, and we could not gather sufficient response rate data for the analyses (online suppl. Fig. S3). Further follow-up was not possible if the patients were transferred to another hospital, which may have overestimated the survival of certain patients because the events were censored. Moreover, we could not optimally compare second-line regimens using methods such as PSM because we did not have sufficient patients per group. Despite these limitations, this study is among the first to report the APAC large-scale outcomes of Ate/Bev treatment and represents the largest number of patients treated with Ate/Bev ever reported, which will reflect patient characteristics and treatment patterns from different countries. Moreover, as no trials have compared second-line options after Ate/Bev failure, this type of study may not be prospectively reported in the near future.

In conclusion, among patients with HCC in APAC countries who discontinued first-line Ate/Bev, approximately half received subsequent treatment. Sorafenib and lenvatinib are the most commonly used second-line regimens, and lenvatinib showed superior survival outcomes compared with sorafenib. The combination of second-line TKI plus ICI exhibited promising efficacy, suggesting the potential role of continuing ICIs beyond disease progression. This large-scale study supports the initiation of a randomized prospective trial of second-line regimens following first-line treatment with Ate/Bev.

Statement of Ethics

The study was reviewed and approved by the Protocol Review Committee of the Korea Cancer Study Group (KCSG HB22-21) and the institutional review boards and ethics committees of each institution. The requirement for informed consent was waived owing to the retrospective nature of the study.

Conflict of Interest Statement

C.-k.L. received honoraria from AstraZeneca, Servier, Dong-A ST, Boryung Pharmaceuticals, and Roche; consulting fees from Roche and Daiichi Sankyo; and research grants or supports from Ono Pharmaceuticals, Celltrion, Boryung Pharmaceuticals, GC Biopharma, and Lunit Inc. C.Y. received honoraria from Servier, Bayer, AstraZeneca, Merck Sharp & Dohme, Eisai, Celgene, Bristol

Myers Squibb, Ipsen, Novartis, Boryung Pharmaceuticals, Mundipharma, and Roche and research grants from Servier, Bayer, AstraZeneca, Ono Pharmaceuticals, Ipsen, Boryung Pharmaceuticals, and Lunit Inc. R.S. is on an advisory board for and receives honoraria for talks from Bristol Myers Squibb; is on an advisory board for and receives fees for travel from Eisai; is on an advisory board for and receives fees for talks and travel from Taiho and DiethelmKellerSiberHegner; is on an advisory board for and receives fees for talks and research funding from Merck Sharp & Dohme; is on an advisory board for Merck, Bayer, Novartis, GlaxoSmithKline, Astellas, Pierre-Fabre, and Tavotek; receives honoraria for talks from Eli Lilly; receives honoraria for talks and travel from Roche, AstraZeneca, and Ipsen; receives research funding and patents from Paxman Coolers; receives research funding from Natera; receives patents from Auristone, outside the submitted work; and has pending patents with Auristone and Paxman. S.L.C. serves as an advisory member for AstraZeneca, MSD, Eisai, BMS, Ipsen, and Hengrui and received research funds from MSD, Eisai, Ipsen, SIRTEX, and Zailab and honoraria from AstraZeneca, Eisai, Roche, Ipsen, and MSD. Hong Jae Chon has a consulting or advisory role at Eisai, Roche, Bayer, ONO, MSD, BMS, Celgene, Sanofi, Servier, AstraZeneca, and GreenCross Cell and has received research grants from Roche, Dong-A ST, and Boryung Pharmaceuticals. The other authors have no conflicts of interest to declare.

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Author Contributions

Prof. Choong-kun Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Choong-kun Lee, Hong Jae Chon, and Myung-Ah Lee. Acquisition, analysis, or interpretation of data and administrative, technical, or material support: Choong-kun Lee, Changhoon Yoo, Jung Yong Hong, Se Jun Park, Jin Won Kim, David Wai Meng Tai, Hyeyeong Kim, Krittiya Korphaisarn, Suebpong Tanasanvimon, San-Chi Chen, Ju Won Kim, Ilhwan Kim, Moonho Kim, Joan Choo, Sang-Bo Oh, Ching-Tso Chen, Woo Kyun Bae, Hongsik Kim, Seok Jae Huh, Chia-Jui Yen, Dong Ki Lee, Landon Chan, Beodeul Kang, Minsu Kang, Raghav Sundar, Hye Jin Choi, Stephen Lam Chan, Hong Jae Chon, and Myung-Ah Lee. Drafting of the manuscript and statistical analysis: Choong-kun Lee. Critical revision of the manuscript for important intellectual content: Choong-kun Lee, Changhoon Yoo, Stephen Lam Chan, Hong Jae Chon, and Myung-Ah Lee. Acquisition, analysis, or interpretation of data and statistical analysis: Sejung Park. Study supervision: Choong-kun Lee, Stephen Lam Chan, Hong Jae Chon, and Myung-Ah Lee.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the first author (C.-k.L.) upon reasonable request.

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