

Efficacy of atezolizumab plus bevacizumab for unresectable HCC: Systematic review and meta-analysis of real-world evidence

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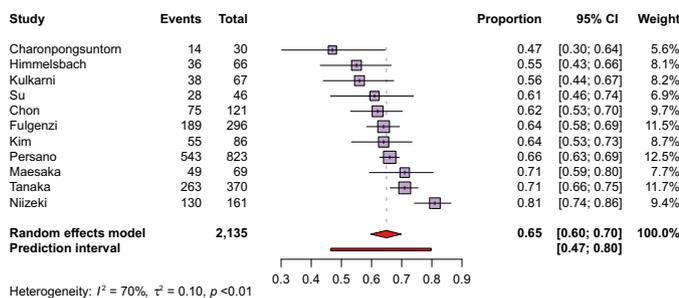
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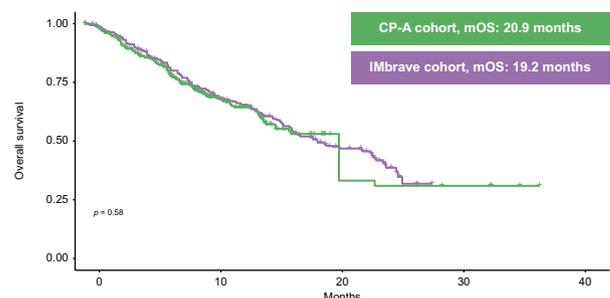
Graphical abstract

A meta-analysis was performed on 2,179 patients selected from 12 cohorts

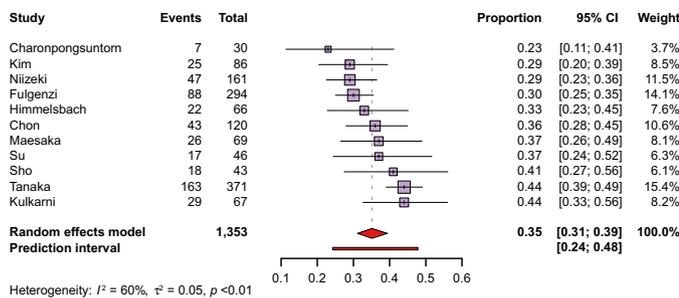
12-month overall survival (OS)



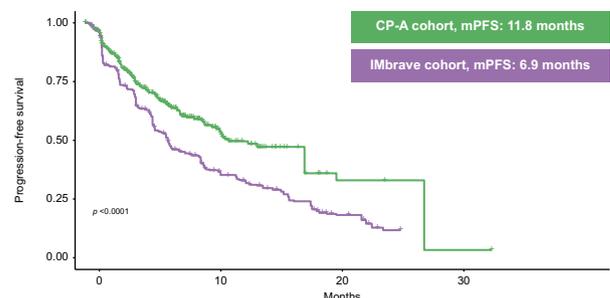
OS between CP-A observational cohort vs. the IMbrave150 cohort



12-month progression-free survival (PFS)



PFS between CP-A observational cohort vs. the IMbrave150 cohort



Highlights:

- Atezolizumab plus bevacizumab (A+B) is associated with 6-/
12-month overall survival probabilities of 82%/65% outside clinical trials.
- Efficacy and tolerability of A+B is consistent with landmark phase III clinical trials in HCC.
- Up to 39% of patients treated with A+B are alive after 24 months, suggesting durable benefit in a proportion of patients with HCC.

Impact and implications:

This study provides real-world evidence supporting the long-term efficacy of atezolizumab plus bevacizumab (A+B) for unresectable hepatocellular carcinoma, showing survival outcomes similar to those achieved in clinical trials. These findings are important for clinicians in supporting A+B as a frontline treatment, particularly for patients with Child–Pugh class A liver function. They also offer valuable insights for policymakers and researchers for optimising treatment strategies for unresectable hepatocellular carcinoma. However, results should be interpreted with caution because of potential variability in patient populations.

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Efficacy of atezolizumab plus bevacizumab for unresectable HCC: Systematic review and meta-analysis of real-world evidence[☆]

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Background & Aims: Atezolizumab plus bevacizumab (A+B) is a standard-of-care treatment in unresectable hepatocellular carcinoma (uHCC). Verification of its effectiveness outside clinical trials is an area of unmet need, especially in estimating long-term survival outcomes.

Methods: We conducted a systematic review and meta-analysis of the MEDLINE, Embase, and Cochrane libraries to evaluate therapy outcomes in patients treated with frontline A+B for uHCC outside trials. Pooled estimates of overall survival (OS) and progression-free survival (PFS) at 6 and 12 months were calculated from individual patient-level data using random-effects analysis.

Results: Of 2,179 patients selected from 12 cohorts, 80.5% were male, median age was 66 years (IQR 61.6–73.0), 61.6% had advanced-stage hepatocellular carcinoma (HCC), and 83.6% were Child–Pugh (CP) class A. Pooled 6- and 12-month OS was 82% (95% CI: 76–86%; $I^2 = 80\%$) and 65% (95% CI: 60–70%; $I^2 = 66\%$). Median OS of patients with CP-A liver function was 20.9 months (95% CI: 15.7–20.9), consistent with IMbrave150 estimates (19.2 months, 95% CI: 17.0–23.7, $p = 0.58$). Pooled PFS at 6 and 12 months was 57% (95% CI: 53–61%; $I^2 = 49\%$) and 35% (95% CI: 31–39%, $I^2 = 60\%$). Among patients with longer follow-up, the OS ($n = 1,783$) and PFS ($n = 959$) rates were 52% (95% CI: 46–58; $I^2 = 90\%$) and 26% (95% CI: 17–37; $I^2 = 91\%$) at 18 months, respectively. At 24 months, OS ($n = 1,556$) rate was 39% (95% CI: 31–49; $I^2 = 90\%$) and PFS ($n = 732$) rate was 25% (95% CI: 12–45; $I^2 = 95\%$).

Conclusions: The effectiveness of A+B after registration mirrors its efficacy estimates from clinical trial datasets. Long-term survival at 24 months can be achieved in up to 39% of patients with uHCC treated with A+B in routine clinical practice.

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Introduction

In 2019, results of IMbrave150 ushered in the era of anti-cancer immunotherapy in unresectable HCC (uHCC) by demonstrating the superiority of atezolizumab plus bevacizumab (A+B) in improving overall (OS) and progression-free survival (PFS) compared with sorafenib in treatment-naïve patients with uHCC.^{1,2} Other first-line systemic options now include durvalumab plus tremelimumab (D+T), proven superior to sorafenib in the HIMALAYA trial, or durvalumab monotherapy, with non-inferior survival compared with sorafenib.³

Although essential for the approval of novel anti-cancer drugs, randomised controlled trials (RCTs) have been called into question for their lack of representation of the broader population of patients with cancer.⁴

This is particularly true for uHCC, where heterogeneity in stage, aetiology, and post-progression therapy significantly impacts OS estimates. Real-world evidence (RWE) provides invaluable insight into the post-registration effectiveness of novel therapies in patients who are not required to fulfil stringent eligibility criteria for RCT enrolment. RWE studies lend an invaluable opportunity to study the uptake and utilisation of therapies in healthcare systems that were not included in registration RCTs.⁵ Since its approval, several reports have documented the use of A+B in patients with uHCC, within and outside the key RCT inclusion criteria. Key limitations of RWE studies remain small sample size, heterogeneous documentation of safety and efficacy outcomes, and high variability in patient eligibility for treatment.

[☆] Given their role as Associate Editor of this journal, AV had no involvement in the peer-review of this article and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to the Guest Editor, Augusto Villanueva.

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To address the limitations of currently available RWE and provide a clinically informative portrait of the utilisation of combination A+B immunotherapy in uHCC, we conducted a meta-analysis to assess whether the post-registration estimates of safety and efficacy mirror those established in the context of phase III RCTs.

In addition, with anti-cancer immunotherapy leading to long-term survivorship in a fraction of patients with uHCC, we attempted to delineate the proportion and characteristics of patients who are free from progression and death beyond 18 months from treatment initiation.

Materials and methods

Search strategy and selection criteria

We conducted a systematic review and single-arm individual patient data (IPD) meta-analysis to compare baseline clinical characteristics and treatment outcomes in patients treated with first-line immune-based therapies for uHCC in routine clinical practice. Although initially planned to focus on the two first-line immune checkpoint inhibitor (ICI) combinations recommended based on the Barcelona Clinic Liver Cancer (BCLC) staging classification 2022 update, namely A+B and D+T, lack of availability of post-registration data on D+T led us to focus exclusively on A+B.

Studies were included in the pooled meta-analysis if: (1) data were collected in a real-world setting; (2) studies considered ICI combinations with A+B as first-line systemic therapy for uHCC; (3) studies evaluated two or more of the following endpoints: OS, PFS, overall response rate (ORR), or disease control rate (DCR) and incidence of treatment-related adverse events (trAEs) graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 or 5 (www.cancer.gov/). Complete inclusion and exclusion criteria, information on the search strategy, and the data extraction are detailed in the supplementary data.

A review and search of the literature was completed using the MEDLINE, Cochrane, and Embase libraries including studies published between January 20, 2019 and September 1, 2023. Conference abstracts were retrieved from major societies in hepatic oncology, including the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), EASL, and AASLD. The meta-analysis protocol was registered in PROSPERO (CRD42023483657). Each study was evaluated for quality according to the Newcastle–Ottawa scale for cohort studies (Table S1). This research was conducted in accordance with the principles of the Declaration of Helsinki. Given that no direct access to identifiable patient-level data was required to conduct this meta-analysis, individual patient consent was waived. Patient consent and research ethics approval were sought and obtained by treating physicians as part of the conduction of each individual study included in this meta-analysis.

Statistical analysis

We performed this meta-analysis using ‘meta’ and ‘metafor’ packages for RStudio, version 4.2.3 (Integrated Development Environment for R, Posit Software, PBC, Boston, MA, USA). IPD were reconstructed from published Kaplan–Meier (KM) survival curves.⁶ Pooled estimates of real-world OS and real-

world PFS at 6, 12, 18, and 24 months were calculated using random-effects analysis. Secondary outcomes included pooled ORR, DCR, and trAEs. Detailed information on data analysis is provided in the supplementary data.

Results

After careful review of the literature, 1,399 reports were identified for the combination of A+B in the target patient population. A flow diagram of the complete literature search is summarised in Fig. S1. In total, 12 studies were eligible for analysis.

Studies characteristics

Characteristics of the 12 eligible studies and their 2,179 patients are summarised in Table 1. All patients received A+B as a first-line systemic therapy with doses consistent with the IMbrave150 trial dosing schedule, except for the study by Su *et al.*⁷ Further details are provided in the supplementary data. The pooled median follow-up estimate in the meta-analysis cohort was 12.9 months (95% CI: 12.4–13.1).

Overall survival analysis

Using individual patient-level data reconstruction from 11 of 12 eligible studies ($n = 2,135$ patients),^{7–18} we analysed pooled OS rates at 6 and 12 months. One study did not provide the OS KM curve and was excluded.¹⁸ The pooled estimate for the 6-month OS rate (Fig. 1A) was 82% (95% CI: 76–86; $I^2 = 80\%$). Considering the heterogeneity in reporting of CP scores across studies, we compared 6-month OS rates in patients who fitted squarely with CP-A cirrhosis in the original studies (Group 1, $n = 385$) against a second group (Group 2, $n = 1,746$), whose survival outcome was not stratified by CP class in the original studies. Group 2 included patients with a wider range of liver dysfunction, including 1,395 CP-A, 136 CP-B, 12 CP-C, 43 patients with a CP score ≥ 7 , and 161 patients without any CP grading. The pooled 6-month OS rate was 83% (95% CI: 78–86; $I^2 = 0\%$) for Group 1 and 80% (95% CI: 70–87; $I^2 = 87\%$) for Group 2, with no statistically significant difference reported across groups ($\chi^2 = 0.31$, $p = 0.57$). The pooled 12-month OS of the entire meta-analysed cohort (Fig. 1B) was 65% (95% CI: 60–70; $I^2 = 70\%$). The 12-month OS rate was 67% in Group 1 and 64% in Group 2, with no difference observed across groups ($\chi^2 = 0.14$, $p = 0.71$). Begg’s funnel plot asymmetry test for 12-month OS demonstrated no publication bias ($p = 0.44$; Fig. S2A).

Using IPD from the updated analysis of IMbrave150,¹ we assessed for differences in median OS across patients receiving A+B on trial ($n = 336$) and those in observational cohorts within Group 1 (*i.e.* CP-A, $n = 385$). No significant difference (Fig. 2A) was found between the median OS of the IMbrave150 cohort (19.2 months, 95% CI: 17.0–23.7) and that of real-world patients classified as CP-A (20.9 months, 95% CI: 15.7–20.9; $p = 0.58$).

We performed an exploratory analysis to evaluate pooled survival estimates at 18 and 24 months, using data from six and four studies, including 1,783 and 1,556 patients, respectively. The pooled 18- and 24-month OS rates were 52% (95% CI: 46–58; $I^2 = 90\%$; Fig. 1C) and 39% (95% CI: 31–49; $I^2 = 90\%$; Fig. 1D), respectively.

Table 1. Studies and patient features.

Study	Design	Country	No. of patients	Median age	Male /female	Non-viral liver disease	CP A/B/C	BCLC 0/A/B/C/D	ECOG PS 0/1-2	Median AFP (ng/ml)	ALBI grade 1/2/3	Varices (no. of patients)	Prior surgery/other LRT	Efficacy outcomes (median OS, PFS, ORR [%], DCR [%])	Median follow-up (months)
Charonpongsuntorn <i>et al.</i> , 2022	P	Thailand	30	58.06	27/3	8	30/0/0	0/0/0/30/0	2/28	770.8	–	18	7/20	10.2, 6.7, 23.3, 63.3	10.1
Chon <i>et al.</i> , 2022	R	Republic of Korea	121	63	100/21	31	109/12/0	0/0/20/101/0	36/85	96	67/54/0	37	33	NR, 5.7, 28.9, 83.4	8.5
Fulgenzi <i>et al.</i> , 2022	R	International	296	66	245/51	101	296/0/0	0/0/92/204/0	139/157 [†]	–	161/133/2	–	83/218	15.7, 6.9, 30.8, 77.7	10
Himmelsbach <i>et al.</i> , 2022	R	Austria, Germany	66	66	54/21	43	35/23/5	0/1/22/35/8	–	17.65	14/46/6	55	9/27	NR, 6.5, 28.8, 62.1	6.9
Kim <i>et al.</i> , 2022	R	Republic of Korea	86	62	70/16	21	82/4/0	0/0/18/68/0	36/50	159	–	60	23/60	NR, 5.7, 32.6, 75.6	7.7
Kulkarni <i>et al.</i> , 2023	R	India	67	61	58/9	43	24/36/7	0/0/6/50/11	40/27	727.3	31/24/12	53	¶¶	12.0, 8.0, 38.7, 66.1	12
Maesaka <i>et al.</i> , 2022	R	Japan	69	74	53/16	33	67/2/0	0/34 A+B/35/0	63/6	17	‡‡	–	–	NR, 8.8, 43.8, 76.6	9.1
Niizeki <i>et al.</i> , 2022	R	Japan	161	73	123/38	76	§	0/4/83/74/0	–	28.3	60/101/0	–	–	NR, 8.3, 44.2, 88.9	12.1
Persano <i>et al.</i> , 2022	R	International	823	‡	657/166	381	769/54/0	0/0/335/488/0	615/208 ^{**}	–	752/66/5	–	***	15.9, NA, 27.3, 79.3	10.4
Sho <i>et al.</i> , 2022 [*]	R	Japan	43	73	38/5	22	43/0/0	0/0/13/30/0	39/4	51.6	17/26/0	–	21	NA, 6.5, 18.4, 81.6	5.6
Su <i>et al.</i> , 2022 [†]	R	Taiwan	46	61.2	38/8	5	40/6/0	0/0/14/32/0	18/28	–	20/§§	–	†††	NR, 5.3, 41.3, 65.2	8.2
Tanaka <i>et al.</i> , 2023	R	Japan	371	74	291/80	220	328/43/0	4/18/142/196/11	300/71 ^{††}	–	144/219/8	–	–	NR, 8.9, 30.6, 81.2	10.4

Continuous variables are reported as median, categorical variables are reported as absolute.

AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; CP, Child–Pugh; ECOG PS, Eastern Cooperative Oncology Group performance status; LRT, locoregional treatments; NA, not available; NR, not reached; P, prospective; R, retrospective.

*Only IMbrave150-in patients were considered.

[†]In this study, bevacizumab was administered at a fixed dose of 500 mg.

[‡]Patients were divided into ≤70 years and >70 years.

[§]No data on CP classes available.

[¶]ECOG PS 1 only.

^{**}ECOG PS ≥1.

^{††}Sixteen patients out of 71 were reported as ECOG PS ≥2, 55 patients as ECOG PS 1.

^{‡‡}Thirty-six patients were classified as ALBI grade 1 or 2a, 33 patients as ALBI 2b or 3, according to modified ALBI.

^{§§}Twenty-three patients were ALBI grade 2 or 3.

^{¶¶}Four transarterial radioembolisation, three transarterial chemoembolisation, one microwave ablation for adrenal metastasis.

^{†††}Prior locoregional therapy included surgery in 569 patients.

^{††††}Twenty-five patients, 14 had combined locoregional therapy.

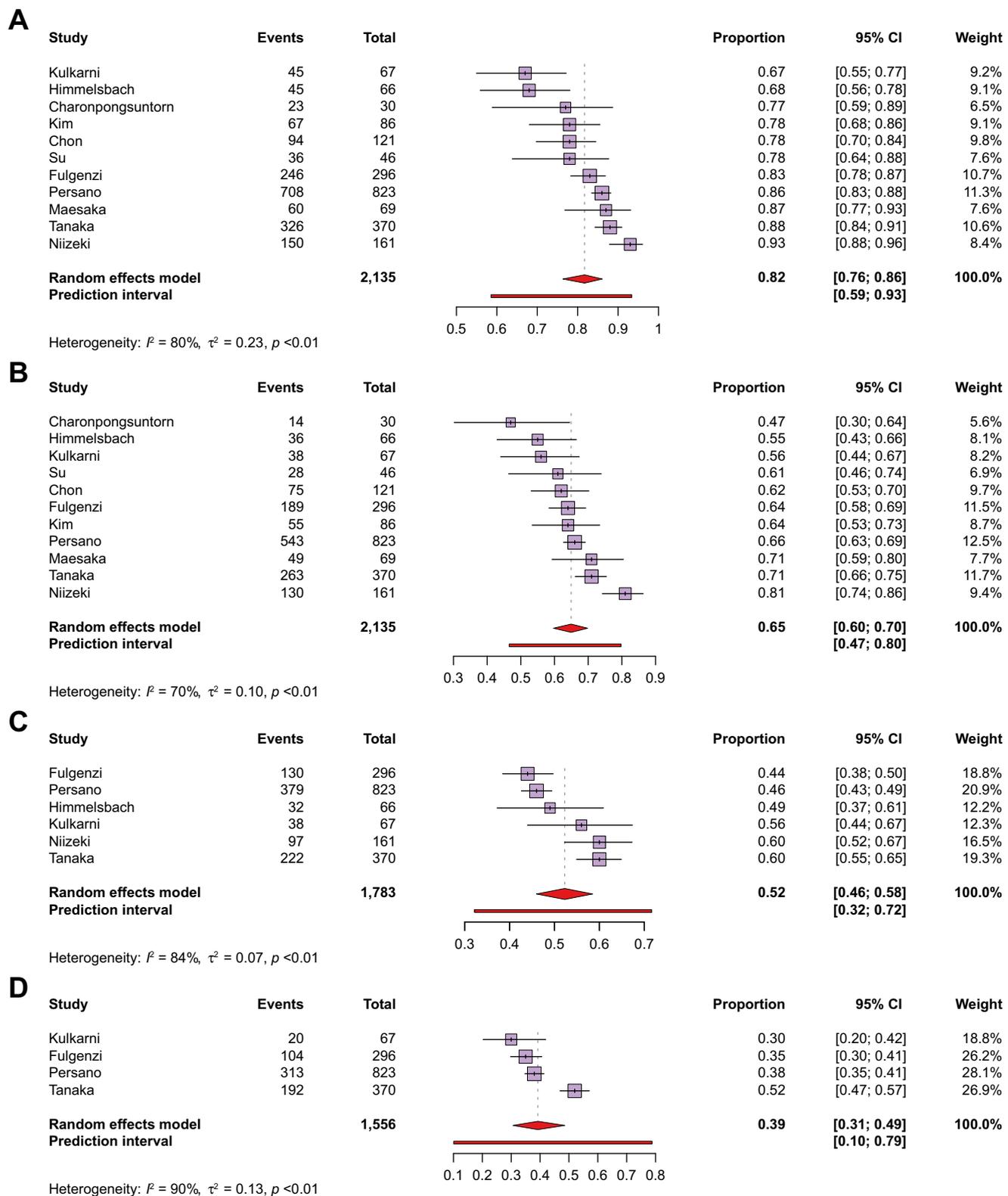


Fig. 1. Forest plots of the pooled OS rates at (A) 6, (B) 12, (C) 18, and (D) 24 months. Lines represent the 95% CI for the OS rate for each considered timeline for each study. Size of squares represents the weight of each study. Diamonds represent the pooled effect. OS, overall survival.

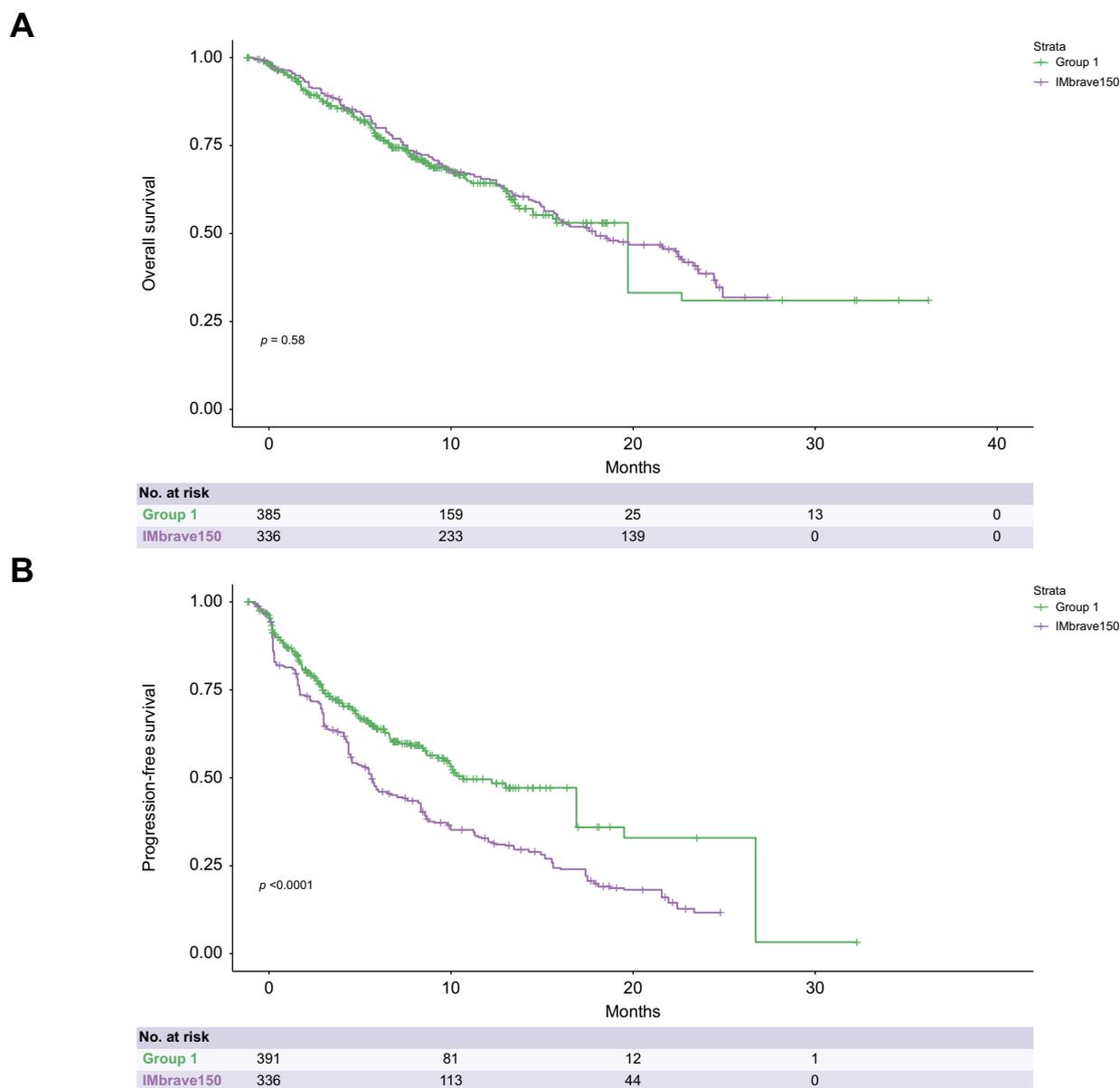


Fig. 2. Comparison of the (A) OS curves and (B) PFS curves from the CP-A observational cohort vs. the IMbrave150 cohort. The median OS of the IMbrave150 cohort was 19.2 months (95% CI: 17.0–23.7), whereas that reported in the real-world cohort was 20.9 months (95% CI: 15.7–20.9) with no significant differences reported between the two cohorts (log rank $p = 0.58$). The median PFS in the real-world cohort was 11.8 months (95% CI: 10.5–18.1), compared with 6.9 months in the IMbrave150 cohort (95% CI: 5.7–8.6; log rank $p < 0.0001$). CP, Child–Pugh; OS, overall survival; PFS, progression-free survival.

Progression-free survival analysis

Data regarding PFS rates could be reconstructed from 11 out of 12 studies^{7,8,10–18} ($n = 1,353$ patients). The pooled PFS at 6 months (Fig. 3A) was estimated at 57% (95% CI: 53–61; $I^2 = 49\%$). We performed a subgroup analysis to compare the pooled 6-month PFS rates based on baseline liver function. We compared 6-month PFS rates in patients who fitted squarely with CP-A cirrhosis in the original studies (Group 3, $n = 391$) against a second group of patients (Group 4, $n = 962$) whose PFS was not stratified by CP class in the original studies. Group 4 included patients with a wider range of liver dysfunction, including 660 classified as CP-A, 125 patients classified as CP-B, 12 classified as CP-C, and 165 patients without CP grade. The pooled 6-month PFS rate was 56% (95% CI: 51–61; $I^2 =$

23%) for Group 3, compared with 57% (95% CI: 52–62; $I^2 = 56\%$) for Group 4. No significant difference was observed across the two groups ($\chi^2 = 0.06$, $p = 0.81$). The pooled 12-month PFS (Fig. 3B) was 35% (95% CI: 31–39; $I^2 = 60\%$), with no significant difference between Groups 3 and 4 ($\chi^2 = 0.16$, $p = 0.69$).

Begg's funnel plot analysis for 12-month PFS demonstrated an absence of relevant publication bias ($p = 0.37$; Fig. S2B). Compared with IPD from the updated analysis of IMbrave150,¹ we assessed for differences in median PFS across patients receiving A+B as part of the registration trial ($n = 336$) and those clustering within Group 3 (i.e. CP-A, $n = 391$). A statistically significant difference was found (Fig. 2B) between the median PFS in patients treated

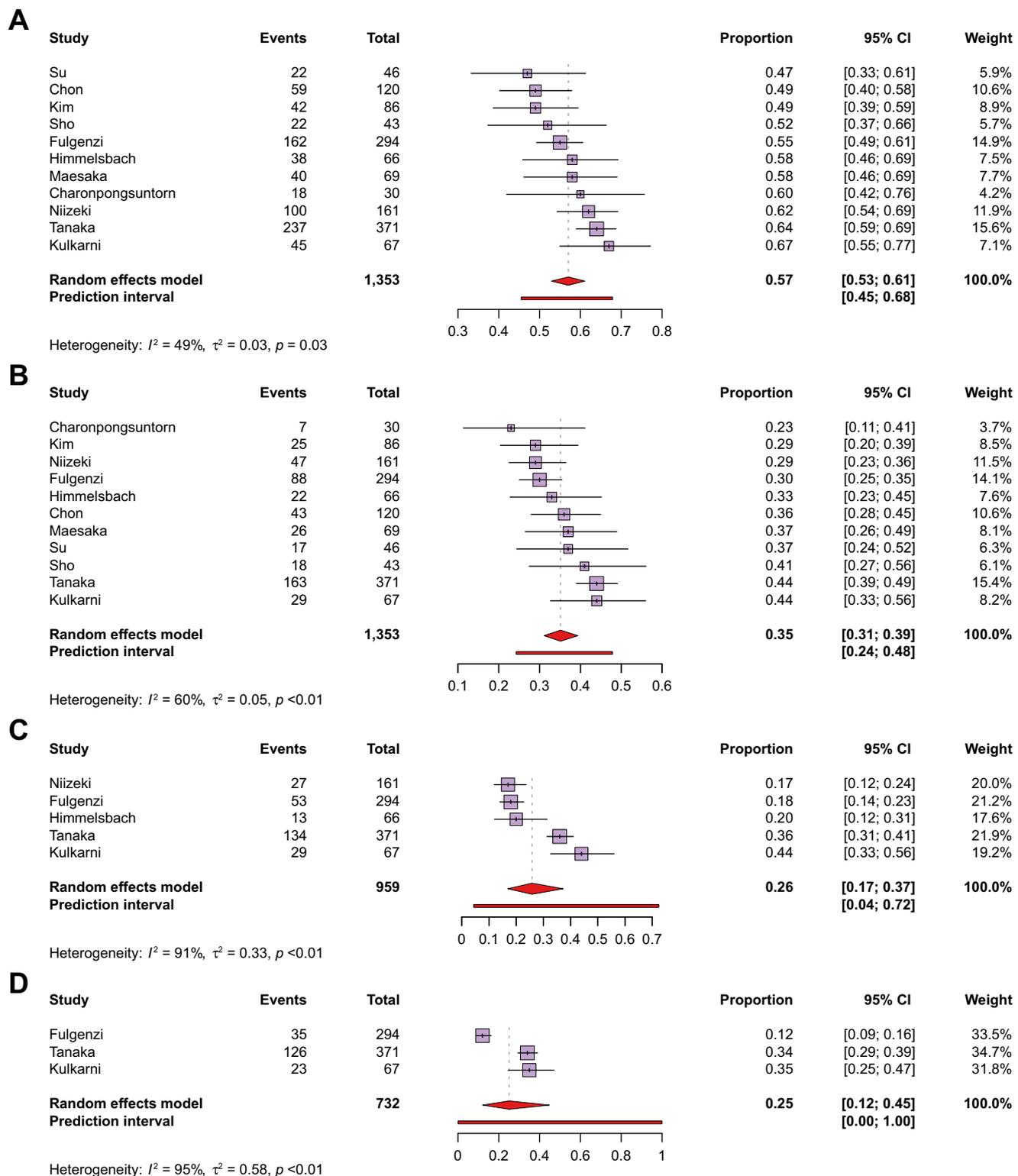


Fig. 3. Forest plots of the pooled PFS rates at (A) 6, (B) 12, (C) 18, and (D) 24 months. Lines represent the 95% CI for the PFS rate for each considered timeline for each study. Size of squares represents the weight of each study. Diamonds represent the pooled effect. PFS, progression-free survival.

outside of clinical trials (11.8 months, 95% CI: 10.5–18.1), compared with the median PFS of IMbrave150 (6.9 months, 95% CI: 5.7–8.6; $p < 0.0001$). The exploratory analyses of the 18- and 24-month PFS rates were possible for six and three

studies (959 and 732 patients, respectively). The pooled 18- and 24-month PFS rates (Fig. 3C,D) were 26% (95% CI: 17–37; $I^2 = 91\%$) and 25% (95% CI: 12–45; $I^2 = 95\%$), respectively.

Radiological response

We reconstructed ORR and DCR data from all eligible studies: in four studies,^{8,13,14,17} response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, whereas in another four studies,^{7,9,10,16} it was assessed by modified (m)RECIST. In the remaining four studies, three compared responses according to both RECIST v1.1 and mRECIST criteria,^{11,12,18} whereas, in the fourth study, response was assessed with either RECIST v1.1 or mRECIST.¹⁵ Radiological response data were reported in individual studies based on the assessment of the treating investigator. Response data were not subject to blinded review or independent verification. When considering patients classified across studies by RECIST v1.1 criteria (n = 1,009), we estimated a pooled ORR of 30% (95% CI: 28–33, I² = 0%) and a pooled DCR of 78% (95% CI: 75–81, I² = 25%; Fig. 4A,B).

We also considered patients classified according to mRECIST criteria (n = 1,337), which led to a pooled ORR of 36% (95% CI: 31–42, I² = 71%; Fig. S3A), and a pooled DCR of 77% (95% CI: 71–82, I² = 67%; Fig. S3B).

Treatment-related adverse events

Occurrence and classification of trAEs were reported in nine studies^{7,8,10–16} (Table 2). In total, 60 different trAEs entries were collectively recorded. A selection of the most reported is listed in Table S2. Seven studies^{7,8,11,12,14–16} reported incidence of trAE rates of any grade, leading to a pooled all-grade trAE rate

of 73% (95% CI: 68–77, I² = 65%). Eight studies^{7,8,11–16} documented the trAEs of grade ≥3, leading to a pooled grade ≥3 trAE rate of 26% (95% CI: 18–36, I² = 83%). Pooled discontinuation rate resulting from toxicity reconstructed from seven eligible studies^{8–11,14–16} was 12% (95% CI 8–18, I² = 66%). Seven deaths as a result of treatment were reported among the 12 studies.

Among atezolizumab-related trAEs, the most reported were fatigue (nine studies), diarrhoea (seven studies),^{7,10–12,14–16} and hypothyroidism (six studies).^{10–14,16} The pooled estimates are shown in Table 2. Liver function test alterations were variably described among studies. Three studies^{7,12,14} reported aspartate and alanine aminotransferase increase separately, whereas three other studies^{11,13,16} reported cumulatively transaminase alterations. One study⁷ reported both alkaline phosphatase and bilirubin increases, and four studies^{12,14–16} reported only bilirubin increases. Three studies^{8,10,15} reported frequency of treatment-related hepatotoxicity, with a pooled rate of any grade hepatotoxicity of 17% (95% CI: 8–35, I² = 81%) and a pooled rate of grade ≥3 hepatotoxicity of 4% (95% CI: 3–7, I² = 0%).

Within bevacizumab-related trAEs, hypertension (nine studies)^{7,8,10–16}, proteinuria (eight studies),^{7,8,10–15} bleeding and gastrointestinal bleeding (seven studies),^{7,8,10,12,14–16} and thromboembolism (five studies)^{8,12–15} were reported. The pooled estimates of the most reported trAEs are shown in Table 2. Variceal bleeding was reported in three studies, with a pooled rate of 9% (95% CI: 2–37, I² = 92%).

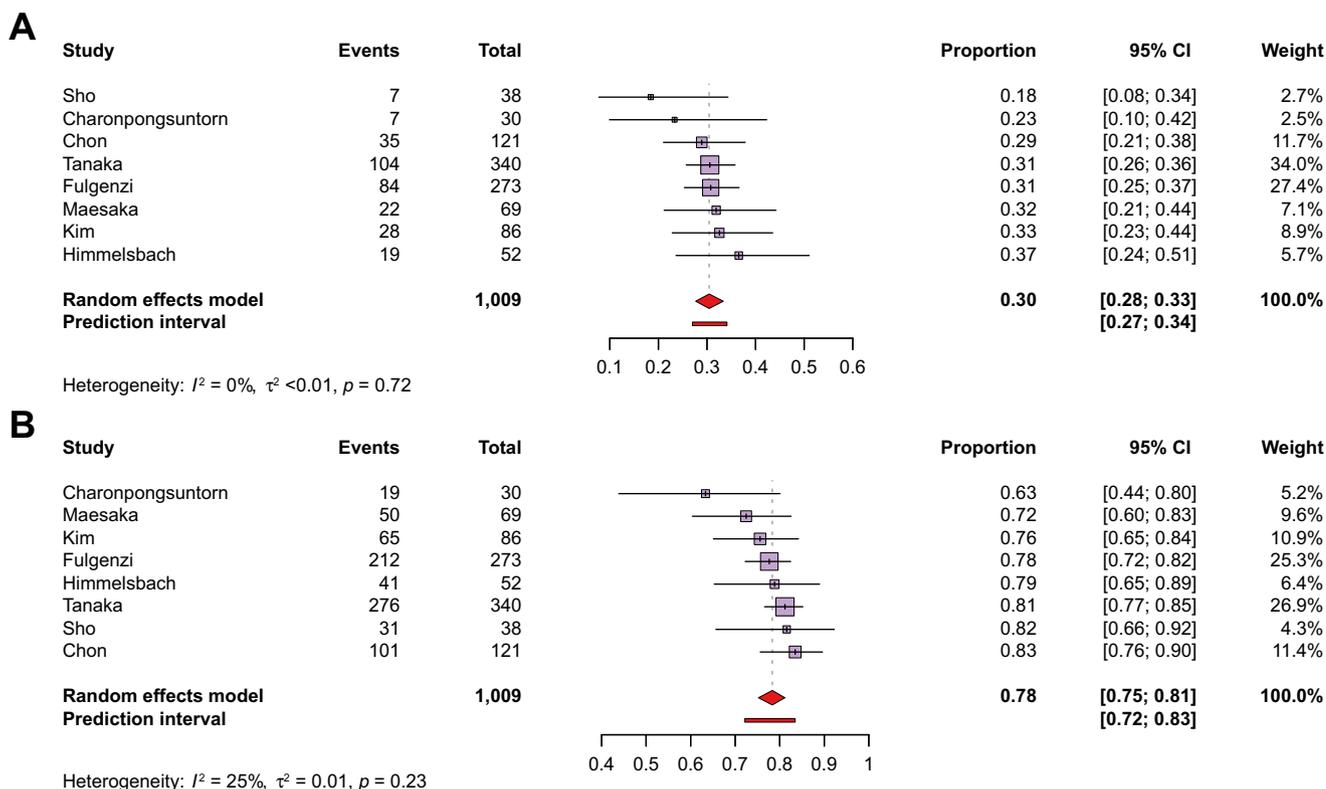


Fig. 4. Forest plots of the (A) pooled ORR and (B) pooled DCR according to RECIST v1.1. Lines represent the 95% CI for the (A) ORR or (B) DCR for each study. Size of squares represents the weight of each study. Diamonds represent the pooled effect. CP, Child–Pugh; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2. Selected treatment-related adverse event frequencies and pooled estimates.

Study	CTCAE (version)	Any trAE, any grade/grade ≥3	Fatigue, any grade/grade ≥3	Hypothyroidism, any grade/grade ≥3	Hypertension, any grade/grade ≥3	Proteinuria, any grade/grade ≥3	GI bleeding, any grade/grade ≥3	Bleeding, any grade/grade ≥3	Diarrhoea, any grade/grade ≥3	trAEs leading to withdrawal	trAEs leading to death
Charonpongsumrit et al., 2022	4	-/6	5/0	13/1	12/2	6/6	-	-	7	0	
Chon et al., 2022	5	85/33	44/0	54/5	35/5	6/4	1/1	6/0	8	-	
Fulgenci et al., 2022	5	221/70	63/2	84/11	90/15	†	25/11	-	25	-	
Himmelsbach et al., 2022	4 + 5	51/39	4/0	3/0	-/-	14/14	20/18	5/2	-	3	
Kim et al., 2022	5	67/19	31/0	36/5	19/1	5/3	1/1	3/0	5	0	
Kulkarni et al., 2023	-	43/14	12/1	5/2	-/-	‡	1/0	1/0	10	-	
Maesaka et al., 2022	4	65/20	24/1	31/7	38/6	-	-	12/0	8	-	
Niizeki et al., 2022*	5	-/-	41/5	15/1	50/9	37/8	15/7	11/1	-	-	
Su et al., 2022	5	29/5	6/0	6/1	3/0	3/3	3/0	3/0	-	1	
Pooled estimates, any grade	-	73% (95% CI: 68-77, I ² = 65%)	23% (95% CI: 16-31, I ² = 78%)	6% (95% CI: 2-14, I ² = 71%)	26% (95% CI: 16-40, I ² = 85%)	8% (95% CI: 4-14, I ² = 78%)	6% (95% CI: 2-14, I ² = 86%)	7% (95% CI: 4-11, I ² = 62%)	4-12% (95% CI: 1-18, I ² = 66%)	-	-
Pooled estimates, grade ≥3	-	26% (95% CI: 18-36, I ² = 83%)	5% (95% CI: 3-7, I ² = 12%)	5% (95% CI: 3-7, I ² = 12%)	8% (95% CI: 4-16, I ² = 80%)	3% (95% CI: 1-6, I ² = 88%)	3% (95% CI: 1-6, I ² = 88%)	10% (95% CI: 6-16, I ² = 88%)	-	-	

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; trAE, treatment-related adverse event.

*AE frequency was reported after propensity score matching.

†Fifteen patients had variceal bleeding.

‡Two patients had grade ≥3 variceal bleeding.

§Only nine cases reported overall.

¶Only one case reported overall.

**Only three cases reported overall.

††Data not available.

Overall, 17 cases of thromboembolic events were recorded across five studies.

Discussion

In our systematic review and meta-analysis of 2,179 patients treated with A+B in the context of observational, real-world studies, the efficacy of A+B was demonstrated by 6- and 12-month OS rates of 82% and 65%, respectively, mirrored by PFS rates at 6 and 12 months of 57% and 35%, respectively.

When considering a large, geographically heterogeneous population of patients with CP-A liver function, OS did not differ significantly from estimates derived from IMbrave150. In our study, PFS estimates from real-world study participants with CP-A liver function were significantly superior to those reported in IMbrave150 (11.8 vs. 6.9 months). We should be mindful that PFS is heavily influenced by the frequency of tumour reassessment. Although most studies reported a frequency of imaging reassessment of the disease every 9–12 weeks following initiation of treatment, the lack of a predefined restaging interval and of centralised and independent review of progression events makes PFS a more labile endpoint in retrospective real-world research. Unlike clinical trials, where progression requires stringent documentation by predefined criteria and poses a strong indication for the discontinuation of treatment, PFS in real-world studies is often a ‘time on treatment’ metric, which reflects the variability among treating physicians in defining progression on clinical grounds and tendency to continue treatment beyond initial progression.¹⁹

Although our primary analysis included patients with impaired liver function, who might derive inferior survival benefit from A+B, the overall radiological response to treatment supports estimates produced in clinical trials, with a pooled ORR of 30% and DCR of 78% according to RECIST v1.1. This is reassuring given the lack of centralised review of response data derived from individual studies included in our meta-analysis, which could impact the reliability of the pooled estimates in case unconfirmed responses were included. Although these concerns remain valid and should guide the interpretation of the efficacy estimates presented in this study, recently published evidence in patients with non-small cell lung cancer provides further reassurance, suggesting an acceptable reliability and reproducibility of response and survival data in well-conducted RWE studies compared with prospective clinical trials.²⁰

Unlike chemotherapy or tyrosine kinase inhibitors (TKIs), anti-cancer immunotherapy can lead to long-term benefit in a fraction of patients. Longer follow-up times in patients treated with D+T in the HIMALAYA study allowed us to determine that 25.2% of patients were alive at 4 years post-treatment initiation²¹; however, no data on the long-term efficacy of A+B exist. Our meta-analysis provides a meaningful contribution to the field, highlighting that up to 52% and 39% of patients who start on A+B remain alive at the landmark timepoints of 18 and 24 months, respectively. These results represent an exploratory analysis that is set to inspire further efforts to study the long-term benefit from A+B. In absence of biomarkers that predict for therapeutic benefit, identification of features related to the achievement of a longer OS could contribute to improved treatment stratification. In addition, further research in this field would be important to inform on the utility of therapy prosecution after the median therapy duration observed in the registration trial.

Most studies included in the meta-analysis also enrolled patients with impaired liver function, confirming the uptake of A+B combination in a broader proportion of patients, compared with those enrolled in RCTs. Whereas patients with CP-C cirrhosis are characterised by poor survival and should be better managed with best supportive care unless meeting liver transplantation criteria, CP-B class includes a highly heterogeneous group of patients. Some might tolerate TKIs¹⁴ and ICI therapy,^{22,23} potentially deriving benefit vs. best supportive care.²⁴ Although prospective studies are underway to evaluate safety and efficacy of ICI in patients with CP-B disease, our data reinforce the safety profile of A+B in patients with CP-A disease by demonstrating estimates of incidence of trAEs that are similar to those described in clinical trials.

Compared with previous meta-analyses,^{25,26} which pooled estimates from RWE plus clinical trials and enrolled patients receiving immunotherapy in later lines, our study is, to the best of our knowledge, the first to apply stringent selection criteria of patients exclusively treated with first-line A+B in routine care.

Despite using stringent eligibility criteria, it is not possible to rule out enrolment of the same patients across different studies. Furthermore, survival outcomes could only be evaluated in 11 studies because of the non-uniform reporting of KM estimates. Limited availability of precise patient-level information on key prognostic covariates, including BCLC stage, CP class, aetiology of chronic liver disease, and other pretreatment factors that might affect outcome should inform a cautious comparative interpretation of efficacy outcomes across observational vs. IMbrave150 study participants. Finally, the pooled analysis of trAEs is heterogeneously based on both unmatched and propensity score-matched populations, depending on the source. Such heterogeneity, combined with the risk of negative ascertainment bias and inconsistent attri-

bution of adverse responses to treatment, should warrant caution in the granular interpretation of trAE data, which might be under-reported, especially for events that are not symptomatic, severe, or rare in incidence.

In addition, uneven and discretionary utilisation of esophago-gastro-duodenoscopy immediately before or within 6 months from the start of A+B, as mandated by IMbrave150,² might have affected the reported pooled incidence of some of the trAEs, including gastrointestinal bleeding, the rates of which were numerically higher compared with prospective clinical trials as a likely result of broader inclusion criteria, including patients beyond CP-A liver dysfunction, less stringently examined for the presence of varices.

Despite including >2,000 patients, our meta-analysis highlights significant gaps in data availability. South America, Australia, and Africa lack RWE representation, a point of greater consequence in establishing efficacy and uptake of novel standards of care on a global scale. In addition, the relatively short median duration of follow-up, which is an essential limitation of pooled real-world data because of the lack of consistent follow-up time, limited our ability to assess the durability of response or make landmark survival estimates beyond the median. Lastly, little information is reported on rates of hepatic decompensation, a clinical scenario associated with poor OS irrespective of treatment efficacy.^{27,28}

In conclusion, our meta-analysis suggests both the reliability and reproducibility of safety and efficacy outcomes from first-line A+B use outside trials. One-third of patients who start A+B remain alive at 24 months, giving important indications of the potential for immunotherapy to lead to long-term benefit in up to 39% of patients. Taken together, these results support A+B-based combination immunotherapy as a contemporary standard of care in uHCC.

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Abbreviations

A+B, atezolizumab plus bevacizumab; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; CP, Child–Pugh; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; D+T, durvalumab plus tremelimumab; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; IPD, individual patient data; KM, Kaplan–Meier; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; RWE, real-world evidence; TKI, tyrosine kinase inhibitors; trAEs, treatment-related adverse events; uHCC, unresectable hepatocellular carcinoma.

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Conflicts of interest

GFM received travel support from Roche. CC received speaker fees and advisory board honoraria from AstraZeneca, Eisai, Merck Sharp & Dohme, and Ipsen, and travel support from Roche. AntD received educational support for congress attendance from Roche, and consultancy fees from Roche, AstraZeneca, and Chugai. MatP received speaker honoraria from Bayer, BMS, Eisai, Ipsen, Lilly, MSD, and Roche; he is a consultant/advisory board member for AstraZeneca,

Bayer, BMS, Eisai, Ipsen, Lilly, MSD, and Roche; he received grants from AstraZeneca, Bayer, BMS, Eisai, and Roche, and travel support from Bayer, BMS, Ipsen, and Roche. BS received grant support (to institution) from AstraZeneca and Eisai, travel support from AbbVie, AstraZeneca, Ipsen, Gilead, and Roche, as well as speaker honoraria from Eisai and AstraZeneca. YHH received honoraria from AstraZeneca, GSK, MSD, Eisai, Gilead, and BMS. AndD received honoraria from AstraZeneca, Eisai, and Roche. AV holds consulting and advisory roles with AbbVie, AstraZeneca, Amgen, BeiGene, Böhringer Mannheim, BMS, Eisai, Incyte, Ipsen, MSD, Pierre Fabre, Roche, Servier, and Tahio. PG received honoraria from Bayer, Boston Scientific, AstraZeneca, Adaptimmune, BMS, Eisai, MSD, Sirtex, Lilly, Roche, Guerbet, and Ipsen. LR reports consulting fees from AbbVie, AstraZeneca, Basilea, Bayer, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, and Zymeworks; lecture fees from AstraZeneca, Bayer, BMS, Guerbet, Incyte, Ipsen, Roche, and Servier; travel expenses from AstraZeneca; and research grants (to institution) from Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Servier, TransThera, and Zymeworks. HJC 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. FP received honoraria from AstraZeneca, Bayer, Bracco, ESAOTE, Eisai, Exact Sciences, GE, Gilead, IPSEN, MSD, Nerviano, Roche, Samsung, and Siemens Healthineers. AP has served on medical advisory boards for Genentech, AstraZeneca, and Exelixis. AGS has served as a consultant or on advisory boards for Genentech, AstraZeneca, Eisai, Bayer, Elevar, Exelixis, Merck, Boston Scientific, Sirtex, HistoSonics, FujiFilm Medical Sciences, Exact Sciences, Roche, Abbott, Glycotest, Freenome, and GRAIL. DJP received lecture fees from ViiV Healthcare, Eisai, IPSEN, and Bayer Healthcare, and travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, Eisai, Roche, IPSEN, DaVolterra, Mursla, and Astra Zeneca; and research funding (to institution) from MSD and BMS.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: GFM, CAMF, DJP. Data acquisition and analysis: GFM, CAMF. Drafting the manuscript: GFM, CAMF, DJP. Critical revision of the manuscript for important intellectual content: all authors.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary data

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Author names in bold designate shared co-first authorship

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