Efficacy and safety of atezolizumab plus bevacizumab as first-line therapy in unresectable Hepatocellular Carcinoma (uHCC) patients with Child-Pugh B compared with Child-Pugh A: A systematic review

by

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Abstract

Background:

Hepatocellular carcinoma (HCC) is one of the forms of primary liver cancer and it accounts for 75-85% of liver cancer cases. The majority of patients in randomized controlled trials (RCTs) of systemic therapy have preserved liver function defined as Child-Pugh class A (CP-A), and it is unknown the treatment effect among CP-B patients. As several real-world studies have started to be reported after the approval of atezolizumab plus bevacizumab (atezo-bev) in unresectable HCC (uHCC), the study aims to conduct a systematic review to build scientific evidence of atezo-bev as a first-line treatment in uHCC with CP-B patients compared with CP-A patients.

Methods:

Two databases (PubMed and EMBASE) were used to search the literature. The search strategies used terms covering atezolizumab AND bevacizumab AND liver. The Critical Assessment Skill Program (CASP) checklist was used to assess the quality of the included studies.

Results:

Four articles were identified as eligible; from these, 346 patients with CP-A and 143 patients with CP-B were identified. The overall response rate (ORR) in CP-B (11.1-40.62%) was similar to the ORR in CP-A (26-45.83%). The median overall survival (mOS) and median progression-free survival (mPFS) were relatively shorter in CP-B than in CP-A (mOS: 16.8-not reached in CP-A vs. 3.3-9 months in CP-B, mPFS: 7.6-18 months in CP-A,

3.0-8 months in CP-B). Notably, two studies concluded there was no significant difference in the incidence of total adverse events (AEs) of any grade and grade ≥3 between CP-A and CP-B. One study also mentioned the number of total AEs of any grade in CP-B was not dissimilar to that in CP-A, while the number of total grade ≥3 AEs was higher in CP-B (44.4% in CP-B vs. 15.8% in CP-A).

Conclusion: The systematic review demonstrated that the new first-line combination therapy of atezo-bev in uHCC with CP-B is distinctly well-tolerable and radiologically effective, though survival time is limited compared with CP-A. More robust evidence based on large prospective studies and even RCTs are necessary to assist selecting uHCC patients who balance efficacy and safety most.

Keywords:

Hepatocellular carcinoma; atezolizumab; bevacizumab; Child-Pugh classification

List of abbreviations

aHCC	Advanced Hepatocellular Carcinoma
AE	Adverse Event
ALBI	Albumin-bilirubin
BCLC	Barcelona Clinic Liver Cancer
CASP	Critical Assessment Skill Program
CP-A	Child-Pugh class A
CP-B	Child-Pugh class B
CP-C	Child-Pugh class C
DCR	Disease Control Rate
EASL	European Association for the Study of the Liver
ECOG-PS	Eastern Cooperative Oncology Group performance status
EMA	European Medical Agency
FDA	Food and Drug Administration
GI	gastrointestinal
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard Ratio
ICI	Immune checkpoint inhibitors
JSH	Japan Society of Hepatology
MHLW	Ministry of Health, Labour and Welfare
mOS	Median Overall Survival

mPFS	Median Progression-Free Survival
mRECIST	modified Response Evaluation Criteria in Solid Tumors
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Mata-analysis
RCTs	Randomized controlled trials
TKI	Tyrosine kinase inhibitors
uHCC	Unresectable Hepatocellular Carcinoma

1. INTRODUCTION

1.1. Background Information

Liver cancer has the sixth highest incidence worldwide and is the third leading cause of cancer death in 2020, with approximately 905,677 new cases and 830,180 deaths (1). In addition, the World Health Organization predicts that incidence rate of liver cancer will increase and that more than 1.4 million people will die from liver cancer by 2040 (2). Both incidence rate and mortality are two to three times higher among men than women in most regions in the world, thus liver cancer ranks second in cause of cancer-related death in men (3).

Hepatocellular carcinoma (HCC) is one of the forms of primary liver cancer and it accounts for 75-85% among liver cancer patients (3). One of the major risk factors for developing HCC is liver cirrhosis. It is known that the prevalence of cirrhosis in HCC patients is about 80-90% (4). Other major risk factors for HCC are hepatitis B or C, alcohol, aflatoxins, diabetes, non-fatty liver disease, autoimmune hepatitis and so on (5). Major risk factors for HCC vary from region to region, with main factors accounting for chronic Hepatitis B virus (HBV) infection and aflatoxin exposure in most high-risk HCC areas like China and Eastern Africa, whereas Hepatitis C virus (HCV) infection is the largest determinant in other countries like Japan (3). In United States, the incidence of HCC is, in part, increasingly related to an increase of obesity and alcohol drinking rates. (6)

The Child-Pugh classification is the standard classification to assess liver function and is classified by the total score of five factors: serum bilirubin and albumin levels, prothrombin time, ascites, and encephalopathy (7,8). According to the Child-Pugh classification, major liver resection, including a right hemi hepatectomy, is possible in Child-Pugh class A (CP-A) patients without cirrhosis, whereas limited resections for small tumors located near the liver

surface are possible in Child-Pugh class B (CP-B) patients and patients with cirrhosis (9).

Systemic therapy is the most recommended therapy for unresectable HCC (uHCC) patients in the advanced stage of the Barcelona Clinic Liver Cancer (BCLC) classification, defined as B and C (10). The majority of patients included in randomized controlled trials (RCTs) of systemic therapy in uHCC were those whose liver functions in a relatively normal manner, CP-A (11). Therefore, the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines states that currently approved systemic treatments are generally safe in patients with uHCC and preserved liver function (ie., CP-A). Due to the lack of inclusion of patients with CP-B in RCTs, the EASL Guidelines pointed out that the treatment benefit is unknown among CP-B patients and an that case-by-case evaluation is required. That also described that safety of both sorafenib and nivolumab in CP-B was partially supported by some cohort studies, but evidence for atezo-bev in CP-B is lacking (10). In most guidelines, systemic therapy is not recommended for patients with the most impaired liver function, defined as CP-C (10-12).

As recommended by ASCO guidelines and EASL Guidelines, the combination therapy of atezo-bev is becoming the new standard-of-care and the first-line treatment for uHCC (10,11). The IMbrave150 trial is a randomized Phase III study looking at the combination therapy of atezolizumab plus bevacizumab (atezo-bev) in uHCC. The study demonstrated that atezo-bev was superior to sorafenib as first-line treatment, showing remarkably better Hazard Ratios (HRs) for Overall Survival (OS) (HR = 0.58, $p = 0.0006$) and Progression-Free Survival (PFS) (HR = 0.59, $p < 0.0001$) (13,14). Regarding systemic agents for uHCC, no drugs had ever shown superiority over sorafenib in 12 years since its approval in 2007. Like other clinical studies, IMbrave150 included patients with good liver function (i.e., patients with CP-A) (13).

Therefore, the present systematic review was performed with real-world studies to create

evidence of atezo-bev as a first-line treatment in uHCC CP-B patients.

1.2. Objectives

Although there are many HCC patients with impaired liver function, little evidence on the safety and efficacy of drug treatment in uHCC patients with CP-B is available, especially of new combination therapy.

As several real-world studies have started to be reported after the approval of atezo-bev in uHCC, the study aims to conduct a systematic review to build scientific evidence of atezo-bev as first-line treatment in uHCC with CP-B patients compared with CP-A patients.

2. METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guideline (15) was used to report the present systematic review.

2.1. Search strategy

The databases (PubMed and EMBASE) were used to search the related literature with the last date of access of 21 Jan 2024. The search strategies used terms covering atezolizumab AND bevacizumab AND liver (appendix A). There were no language restrictions. Reviews, case reports, case series, editorials, guidelines, correspondences, conference abstracts, RCTs, systematic reviews, and meta-analysis were not considered.

Prospective and retrospective cohort studies were included, targeting uHCC and comparing treatment outcome among patients with CP-A and CP-B. Studies having the treatment outcome of atezo-bev by CP classification at a first-line therapy setting were also included.

Animal experiments, exploratory mechanism-finding studies, cost-effective analysis, AI-based studies, and studies including other disease than HCC were excluded. Studies that compare the results between atezolizumab plus bevacizumab versus other drugs such as Immune checkpoint inhibitors (ICI) or Tyrosine kinase inhibitors (TKI) were also excluded.

2.2. Data extraction

For each study, the number of patients per CP classification, age, sex, etiology, BCLC stage, Eastern Cooperative Oncology Group performance status (ECOG-PS), and albumin-bilirubin (ALBI) stage were retrieved.

For efficacy assessment, median OS (mOS), median PFS (mPFS), Overall Response Rate (ORR), and/or Disease Control Rate (DCR), whichever is available in the included study, were extracted. For safety assessment, any Adverse Event (AE) information available was retrieved. The characteristics and the results of the included studies were summarized in tables.

2.3. Quality assessment

The Critical Assessment Skill Program (CASP) checklist was used to assess the quality of the included studies. CASP checklist consists of 10 questions about validity of the results, the result contents, and the ability of the results application to the local population (16).

3. RESULTS

3.1. Studies included and patient characteristics

Four articles were identified as eligible (17-20). In total, 346 patients with CP-A, 143 patients with CP-B were included. In one of the included studies, Himmelsbach V et al. (2022) could not obtain the CP assessment results for four patients (20). The number of countries where these studies were conducted differed from study to study; for instance, D'Alessio A et al. (2022), included 7 countries, and Himmelsbach V et al. (2022), included 2 countries, while Cheon J et al. (2023) and Kulkarni et al. (2023) recruited patients only in South Korea and India, respectively (17-20). All these studies reported real-life treatment outcome of atezo-bev at first-line setting in uHCC. The dosing of atezo-bev (atezolizumab 1200 mg plus bevacizumab 15 mg/kg intravenously every 3 weeks) in all of the included studies was based on the IMbrave150 trial protocol. Atezo-bev treatment continued till

patients experienced intolerable toxicity, disease progression, death, or liver transplantation. Frequency and criteria of radiological assessment differed among studies; every 9-12 weeks with the Response Evaluation Criteria in Solid Tumors (RECIST) criteria v.1.1 in the study by D'Alessio A et al. (2022), every 6-8 weeks with RECIST v.1.1 in the study by Cheon J et al. (2023) (17,18). Kulkarni AV et al. (2023) assessed after 3-4 cycles of immunotherapy using the modified Response Evaluation Criteria in Solid Tumors (mRECIST), which is common for HCC assessment (19) . Himmelsbach V et al. (2022) chose the RECIST v.1.1 or mRECIST v.1.1 based on their institutions' preference, and the response was recorded at baseline, 6-12 weeks after treatment initiation, and 2-3 months thereafter according to the local guidelines (20). D'Alessio A et al. (2022) assessed adverse events at every contact with patients and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v.5.0, where only AEs related to the treatment were collected. Cheon J et al. (2023) graded the treatment-related adverse events according to the CTCAE v.5.0, but the frequency of AE assessment was not mentioned. Kulkarni AV et al. (2023) reported AEs were managed based on the hospital protocol and as described by the summary of the product characteristics (18,19). Himmelsbach V et al. (2022) reported side effects at every visit and graded them according to CTCAE v.4.0 or v.5.0 based on their institutions' choice (20).

Among the four studies, age range and sex distribution were similar. Etiology was different from study to study, which is supposed to be affected by the geographical area where each study conducted. The study by Cheon J et al. (2023) has the highest prevalence of hepatitis B with 69.2% in CP-A and 58.3% in CP-B (18). The majority of patients in each study were at the BCLC stage C, ECOG-PS 0. Most of the patients were graded as ALBI grade 2 in the study by D'Alessio A et al. (2022) and Himmelsbach et al. (2022) (17,20). Kulkarni AV et al. (2023) included patients with healthier ALBI grade (46.3% at grade 1 vs.

35.8% at grade2) (19).

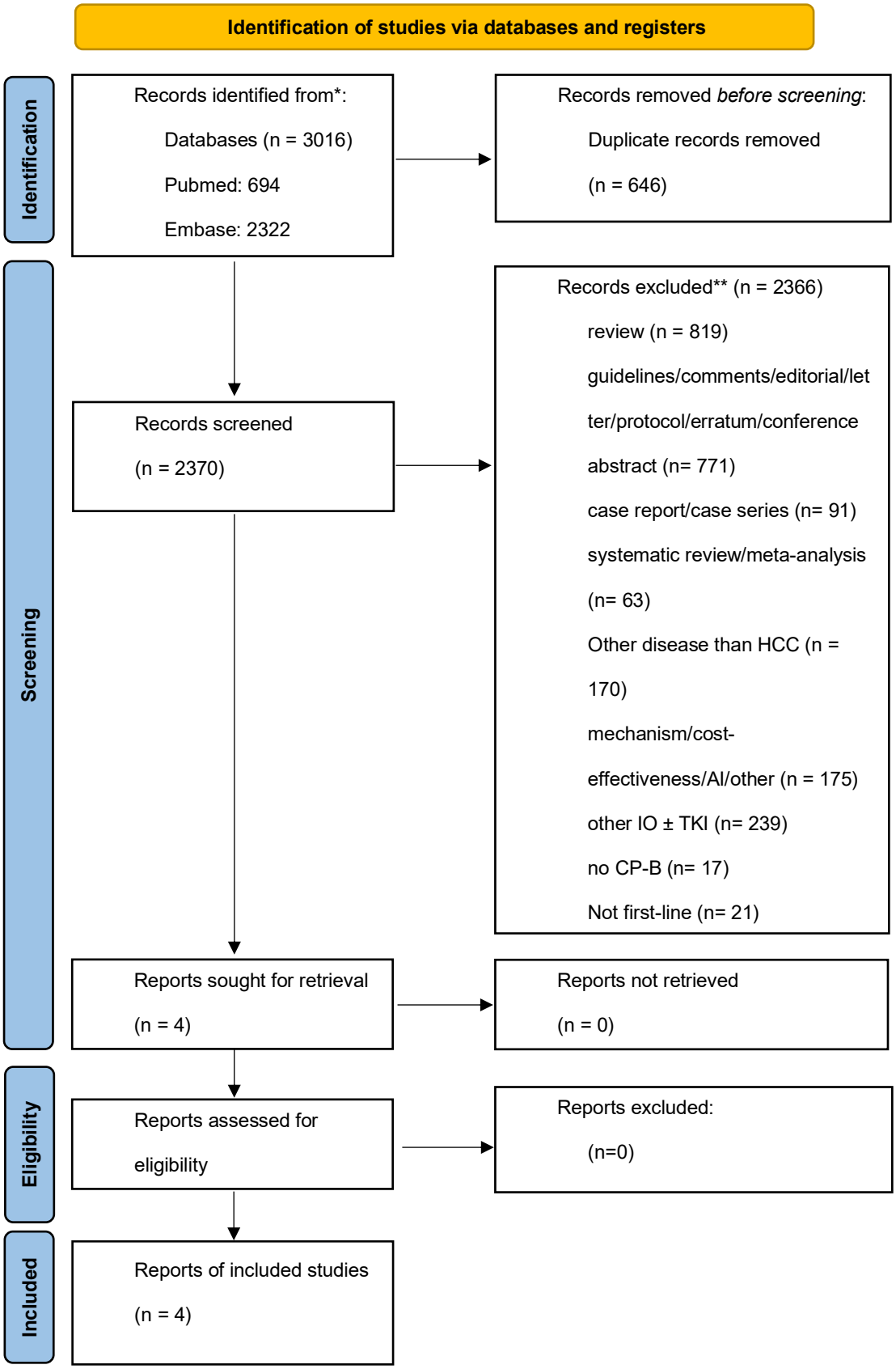

Figure 1: PRISMA Flowchart

3.2. Efficacy

The mOS for CP-A was 16.8-21 months in two studies, and the other two studies indicated that mOS was not reached, while the mOS for CP-B was 3.3-9 months among the four included studies (17-20). The mPFS was 7.6-18 months for CP-A, 3.0-9 months for CP-B in three studies (17-19). Two studies reported that there was no significant difference between CP-A and CP-B in terms of ORR (26% vs 21% and 45.83% vs. 40.62%) (17,19), but one study reported higher ORR in CP-A (34.1%) than the ORR in CP-B (11.1%, p=0.007) (18). The DCR reported 74-79.16% in CP-A and 58.3-69.75% in CP-B (17-19). Himmelsbach V et al. (2022) has no data of mPFS, ORR and DCR (20).

3.3. Safety

D'Alessio A et al. (2022) reported no difference was observed in terms of toxicity. Bevacizumab-related AEs of both any grade and grade ≥3 were proportionate between CP-A and B (48% vs. 46% for any grade, 16% vs. 15% for grade ≥3). The incidence of gastrointestinal (GI) bleeding events was similar in CP-A and CP-B when considering events of any grade (14% vs. 15%) and grade ≥3 (4% vs. 10%). CP-A patients experienced atezolizumab-related AEs of any grade (53%) and grade ≥3 (40%) with similar rates to those with CP-B (40% for any grade, 4% for grade ≥3) (17).

Cheon J et al. (2023) also reported that the overall incidence of any AEs was comparable between CP-A and CP-B (88.7% vs. 97.2%, p=0.198), but grade ≥3 AEs were more frequent in CP-B (15.8% vs. 44.4%, p<0.001). The incidence of hypertension of any grade was higher in CP-A (54.1%) than in CP-B (16.7%) (p<0.001). The study demonstrated that CP-B patients have significantly higher risk of some AEs (see Table 3) (18).

Kulkarni AV et al. (2023) showed no significant difference between CP-A and CP-B of

the incidence of any grade AEs (62.5% vs. 61.1%) and of grade ≥3 AEs (12.5% vs. 14%). Two rises in bilirubin (>3 mg/dl), one hypertension and two ascites were reported in CP-B, whereas one rise in bilirubin and none of hypertension nor ascites were reported in CP-A. Two CP-A patients experienced variceal bleed, while none of CP-B patients did (19).

The study of Himmelsbach V et al. (2022) showed no adverse event incidence per CP classification (20).

Table 1: Characteristics of the included studies

No.	Name, Country, Year	Total N	Child class N (%)	Age Year (range)	Sex, males N (%)	Etiology	BCLC stage	ECOG-PS	ALBI grade
1	D'Alessio A et al., Germany, United States, Japan, Austria, United Kingdom, Italy, and Taiwan, 2022 (17)	202	CP-A: 154 (76%) CP-B: 48 (24%)	69 (23-90)	173 (85%)	HBV: 35 (17%) HCV: 72 (36%) HBV and HCV: 3 (1%) Alcohol: 39 NASH: 23 Cryptogenic: 30	A: 3 (2%) B: 55 (27%) C: 144 (71%)	0: 127 (63%) 1: 70 (35%) 2: 5 (2%)	1: 71 (35%) 2: 118 (59%) 3: 13 (6%)
2	Cheon J et al., South Korea, 2023 (18)	169	CP-A: 133 (78.7%)	62.0 (34.0-90.0)	109 (82.0%)	Hepatitis B: 92 (69.2%) Hepatitis C: 6 (4.5%) Alcohol: 19 (14.3%) Unknown: 16 (12.0%)	B: 26 (19.5%) C: 107 (80.5%)	0/1: 131 (98.5%) 2: 2 (1.5%)	1: 91 (68.4%) 2: 42 (31.6%) 3: 0 (0.0%)
			CP-B: 36 (21.3%)	61.0 (42.0-85.0)	30 (83.3%)	Hepatitis B: 21 (58.3%) Hepatitis C: 5 (13.9%) Alcohol: 6 (16.7%) Unknown: 4 (11.1%)	B: 10 (27.8%) C: 26 (72.2%)	0/1: 31 (86.1%) 2: 5 (13.9%)	1: 2: (5.6%) 2: 30 (83.3%) 3: 4 (2.4%)
3	Kulkarni AV et al., India, 2023 (19)	67	CP-A: 24 (35.8%) CP-B: 36 (53.7%) CP-C: 7 (10.4%)	61 (29-82)	58 (86.5%)	HBV: 13 (19.4%) HCV: 11 (16.4%) Alcohol: 5 (7.5%) NASH: 37 (55.2%) Cryptogenic: 1 (1.5%)	B: 6 (9%) C: 50 (74.6%) D: 11 (16.4%)	0: 40 (59.7%) 1: 27 (40.3%)	1: 31 (46.3%) 2: 24 (35.8%) 3: 12 (17.9%)
4	Himmelsbach V et al., Germany, Austria, 2022 (20)	66	CP-A: 35 (53.0%) CP-B: 23 (34.8%) CP-C: 5 (7.6%) Unknown: 4 (6.1%)	65 (30-88)	54 (81.8%)	Hepatitis B: 9 (13.6%) Hepatitis C: 14 (21.2%) NASH/NAFLD: 18 (27.3%)	A: 1 (1.5%) B: 22 (33.3%) C: 35 (53.0%) D: 8 (12.1%)	No data	1: 14 (21.2%) 2: 46 (69.7%) 3: 6 (9.1%)

Table 2: Efficacy profile of the included studies

No.	Name, Year	mOS Months (95% CI)		mPFS Months (95% CI)		ORR %		DCR %	
		CP-A	CP-B	CP-A	CP-B	CP-A	CP-B	CP-A	CP-B
1	D'Alessio A et al., 2022 (17)	16.8 (14.1-23.9)	6.7 (4.3-15.6) (p=0.0003)	7.6 (6.2-8.9)	3.4 (2.6-4.2) (p=0.03)	26%	21%	74%	68%
2	Cheon J et al., 2023 (18)	Not reached	7.7 (p<0.001)	9.6	3.0 (p<0.001)	34.1%	11.1% (p=0.007)	76.7%	58.3% (p=0.036)
3	Kulkarni AV et al., 2023 (19)	21 (0-42.06)	9 (5.46-12.53)	18 (0.16-35.84)	8 (6.14-9.85)	45.83%	40.62%	79.16%	69.75%
4	Himmelsbach V et al., 2022 (20)	Not reached	3.3	No data	No data	No data	No data	No data	No data

Table 3: Safety profile of the included studies

No.	Name, Year	AE type	Any grade			Grade ≥3		
			CP-A	CP-B	P value	CP-A	CP-B	P value
1	D'Alessio A et al., 2022 (17)	Bevacizumab-related AEs	74 (48%)	22 (46%)	>0.05 for all associations	24 (16%)	7 (15%)	>0.05 for all associations
		GI bleeding	22 (14%)	7 (15%)		6 (4%)	5 (10%)	
		Atezolizumab-related AEs	82 (53%)	19 (40%)		23 (15%)	2 (4%)	
		Atezolizumab-related hepatitis	23 (15%)	5 (10%)		12 (8%)	0 (0%)	
2	Cheon J et al., 2023 (18)	Total	118 (88.7%)	35 (97.2%)	0.198	21 (15.8%)	16 (44.4%)	<0.001
		Hypertension	72 (54.1%)	6 (16.7%)	<0.001	6 (4.5%)	1 (2.8%)	0.643
		GI hemorrhage	4 (3.0%)	6 (16.7%)	0.002	1 (0.8%)	6 (16.7%)	<0.001
		Neutropenia	27 (20.3%)	9 (25.0%)	0.541	0 (0%)	5 (13.9%)	<0.001
		Thrombocytopenia	54 (41.2%)	14 (38.9%)	0.801	1 (0.8%)	4 (11.1%)	0.001
		Hyperbilirubinemia	23 (17.3%)	23 (63.9%)	<0.001	0 (0%)	2 (5.6%)	0.006
3	Kulkarni AV et al., 2023 (19)	Total	15 (62.5%)	22 (61.1%)		3 (12.5%)	5 (14%)	-
		Rise in bilirubin (>3 mg/dl)	-	-	-	1 (4.2%)	2 (5.6%)	-
		Variceal bleed	-	-	-	2 (8.3%)	0	-
		Ascites	-	-	-	0	2 (5.6%)	-
4	Himmelsbach V et al., 2022 (20)	No data	-	-	-	-	-	-

3.4. Quality Assessment

Studies were appraised for quality in accordance with the CASP cohort study checklist (see Table 4).

Table 4: Quality assessment using CASP checklist for cohort study

	1	2	3	4
	D'Alessio A et al., 2022 (17)	Cheon J et al., 2023 (18)	Kulkarni AV et al., 2023 (19)	Himmelsbach V et al., 2022 (20)
1. Did the study address a clearly focused issue?	Yes	Yes	Yes	Partially yes
2. Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes
3. Was the exposure accurately measured to minimize bias?	Yes	Yes	Yes	Yes
4. Was the outcome accurately measured to minimize bias?	Yes	Yes	Yes	Yes
5. a) Have the authors identified all important confounding factors? b) Have they taken account of the confounding factors in the design and/or analysis	a) Can't tell b) No	a) Can't tell b) No	a) Can't tell b) No	a) Can't tell b) No
6. a) Was the follow up of subjects complete enough? b) Was the follow up of subjects long enough?	a) Yes b) Yes	a) No b) No	a) Yes b) Yes	a) No b) No
7. What are the results of this study?	See Table 1-3	See Table 1-3	See Table 1-3	See Table 1-3
8. How precise are the results?	Not precise	Precise enough	Precise enough	Not precise
9. Do you believe the results?	Yes	Yes	Yes	Yes
10. Can the results be applied to the local population?	Yes	Yes	Yes	Yes
11. Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes
12. What are the implications of this study for practice?	Yes	Yes	Yes	Yes

4. DISCUSSION

The new combination therapy of atezo-bev was approved in 2020 by the Food and Drug Administration (FDA), the European Medical Agency (EMA) and the Ministry of Health, Labour and Welfare (MHLW). Real-world data to examine the outcome of atezo-bev in a vulnerable population has been emerging after the approvals.

In the systematic review with data from four studies including 346 patients with CP-A and 143 patients with CP-B, the ORR in CP-B (11.1-40.62%) was similar to the ORR in CP-A (26-45.83%). The DCR also showed comparable data, which was 58.3-69.75% in CP-B vs. 74-79.16% in CP-A. The mOS and mPFS were relatively shorter in CP-B than in CP-A (mOS: 16.8-not reached in CP-A vs. 3.3-9 months in CP-B, mPFS: 7.6-18 months in CP-A, 3.0-8 months in CP-B). Notably, two studies concluded there was no significant difference in the incidence of total AEs of any grade and grade ≥3 between CP-A and CP-B. One study also mentioned that the number of total AEs of any grade in CP-B was not dissimilar to that in CP-A, while the number of total grade ≥3 AEs was higher in CP-B (44.4% in CP-B vs. 15.8% in CP-A) (17-20).

Considering the median survival of untreated aHCC with CP-B of 5 months (21), this study showed that first-line atezo-bev could be beneficial even to some CP-B uHCC patients.

In the updated IMbrave150 analysis, which is a pivotal study of atezo-bev in first-line setting and only recruits CP-A in terms of CP class, mPFS and mOS were reported as 6.9 month (5.7-8.6 months) and 19.2 months (17.0-23.7 months), respectively, and the ORR was reported as 30% (25-35%) (14), which confirms the studies by D'Alessio A et al. (2022) and Cheon J et al. (2023) (17,18). Only Kulkarni AV et al. (2023), reported longer PFS of 18 months and higher ORR of 45.83% in CP-A compared with the updated IMbrave150 results (14,19). Compared with the background of CP-A patients from the four included studies and

the IMbrave150 study, there was no meaningful difference (14,17-20).

Bevacizumab is known to increase the risk of serious hemorrhage in cancer patients (22). In the study, Cheon J et al. (2023), pointed out that GI hemorrhage events of both any grade and grade ≥3 were high in CP-B compared with CP-A (18). This suggests the necessity of further investigation on who can avoid the feared complication of bevacizumab in patients with CP-B, and what kind of preventive actions doctors can take.

Sorafenib was approved by the FDA in 2007 for use in patients with uHCC. The GIDEON trial that was a prospective, observational registry study was initiated from Jan 2009 to gather more comprehensive data on the use of sorafenib in patients with CP-B liver function in real-life practice. The GIDEON study concluded with 3202 patients' data that the safety profile of sorafenib was consistent across CP-A and CP-B although median overall survival was longer in CP-A compared with CP-B (13.6 vs 5.2 months) (23). Similar observational studies would be necessary for atezo-bev to better understand the risk benefit in CP-B comparing with CP-A.

CP-B patient fragility is heterogeneous depending on the numeric score such as B7, B8, or B9. Piscaglia et al. (2013), reported that median survival of the intermediate patients was longer in CP-B7 compared with CP-B8 and CP-B9 (9.0 vs 6.0 months, P=0.048) and that the CP numeric score impacts survival even among CP-B (24). Kudo et al. (2021), reported the result of CP-B cohort in the CheckMate040 study, which is considered to be the first prospective study of immunotherapy in patients with CP-B advanced HCC (aHCC). CheckMate040 study was to investigate efficacy and safety of nivolumab in uHCC and they allowed to include only CP-B7 and B8 in the cohort. They concluded that Nivolumab has a favorable safety profile in CP-B7/B8 and is comparable to CP-A. Notably, mOS with nivolumab was longer than the historical OS with sorafenib in CP-B (7.6 vs 2.5-5.4 months) (25). Further investigation is required to see which treatment would be the best as a first

choice for CP-B uHCC patients.

4.1. Limitations

The study includes some limitations. First of all, only four articles were included in the study, which was not enough for meta-analysis. Second, there were some missing data in some studies such as numeric score of Child-Pugh Classification, detailed AEs, as well as ORR and DCR. Third, the search strategy will limit subgroup analysis data of CP-A and CP-B in studies on first-line atezo-bev and that may have led to the missing of some potentially important findings. Fourth, publication bias as well as still limited real-world data just after the treatment approvals should be taken into consideration.

4.2. Conclusions

The systematic review demonstrated that the new first-line combination therapy of atezo-bev in uHCC with CP-B is distinctly well-tolerable and radiologically effective, though survival time is limited compared with CP-A. The findings support atezo-bev as another treatment option for patients who have more impaired liver function, but more robust evidence based on large prospective studies and even RCTs are necessary to assist doctors in selecting uHCC patients who balance efficacy and safety most.

5. References

(1) Cancer Today. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. Accessed Nov 5, 2023.

(2) Cancer Tomorrow. Available at: https://gco.iarc.fr/tomorrow/en/dataviz/isotype?cancers=11&single_unit=50000. Accessed Nov 5, 2023.

(3) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018 -11;68(6):394-424.

(4) Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012 -03-31;379(9822):1245-1255.

(5) Gomaa A, Khan S, Toledano M, Waked I, Taylor-Robinson S. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. World J Gastroenterol 2008 -07-21;14(27):4300-4308.

(6) Islami F, Miller KD, Siegel RL, Fedewa SA, Ward EM, Jemal A. Disparities in liver cancer occurrence in the United States by race/ethnicity and state. CA Cancer J Clin 2017 -07-08;67(4):273-289.

(7) Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg 1964;1:1-85.

(8) Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973 -08;60(8):646-649.

(9) Norihiro Kokudo KH. Blumgart's Surgery of the Liver, Biliary Tract and Pancreas, 2-Volume Set (Sixth Edition). Volume 2 ed.; 2017.

(10) Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: An EASL position paper. J Hepatol 2021 -10;75(4):960-974.

(11) Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. J Clin Oncol 2020 -12-20;38(36):4317-4345.

(12) Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, et al. Management of Hepatocellular Carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update. Liver Cancer 2021 -6;10(3):181-223.

(13) Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020 -05-14;382(20):1894-1905.

(14) Cheng A, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022 -04;76(4):862-873.

(15) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021 -03-29;372:n71.

(16) Critical Appraisal Skills Programme checklist. Available at: https://casp-uk.net/images/checklist/documents/CASP-Systematic-Review-Checklist/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf. Accessed May 5, 2023.

(17) D'Alessio A, Fulgenzi CAM, Nishida N, Schönlein M, von Felden J, Schulze K, et al. Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: A real-world study. Hepatology 2022 -10;76(4):1000-1012.

(18) Cheon J, Kim H, Kim HS, Kim CG, Kim I, Kang B, et al. Atezolizumab plus bevacizumab in patients with child-Pugh B advanced hepatocellular carcinoma. Ther Adv Med Oncol 2023 January 12;15:17588359221148541.

(19) Kulkarni AV, Krishna V, Kumar K, Sharma M, Patodiya B, Khan A, et al. Safety and Efficacy of Atezolizumab-Bevacizumab in Real World: The First Indian Experience. J Clin Exp Hepatol 2023;13(4):618-623.

(20) Himmelsbach V, Pinter M, Scheiner B, Venerito M, Sinner F, Zimpel C, et al. Efficacy and Safety of Atezolizumab and Bevacizumab in the Real-World Treatment of Advanced Hepatocellular Carcinoma: Experience from Four Tertiary Centers. Cancers (Basel) 2022 -03-28;14(7):1722.

(21) Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology 2015 -01;61(1):184-190.

(22) Hapani S, Sher A, Chu D, Wu S. Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology 2010;79(1-2):27-38.

(23) Marrero JA, Kudo M, Venook AP, Ye S, Bronowicki J, Chen X, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol 2016 -12;65(6):1140-1147.

(24) Piscaglia F, Terzi E, Cucchetti A, Trimarchi C, Granito A, Leoni S, et al. Treatment of hepatocellular carcinoma in Child-Pugh B patients. Dig Liver Dis 2013 -10;45(10):852-858.

(25) Kudo M, Matilla A, Santoro A, Melero I, Gracián AC, Acosta-Rivera M, et al. CheckMate 040 cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. J Hepatol 2021 -09;75(3):600-609.

Appendix A: Search strategy

Pubmed:

(bevacizumab [MeSH Terms] OR bevacizumab OR Avastin) AND (atezolizumab [Supplementary Concept] OR atezolizumab OR Tecentriq) AND (liver [MeSH Terms] OR liver OR hepatocellular)

Embase:

('bevacizumab'/exp OR 'bevacizumab' OR avastin) AND ('atezolizumab'/exp OR 'atezolizumab' OR tecentriq) AND (liver OR hepatocellular)