Liver Cancer

Meta-Analysis

Liver Cancer 2024;13:235–245
DOI: 10.1159/000533991

Received: May 24, 2023
Accepted: September 4, 2023
Published online: October 14, 2023

Safety and Efficacy of Atezolizumab/Bevacizumab in Patients with Hepatocellular Carcinoma and Impaired Liver Function: A Systematic Review and Meta-Analysis

Andrea Pasta[a, b] Francesco Calabrese[a, b] Ariel Jaffe[c, d] Sara Labanca[a, b] Simona Marenco[a, b] Giulia Pieri[a, b] Maria Corina Plaz Torres[a, b] Mario Strazzabosco[c, d] Edoardo G. Giannini[a, b, c]

[a]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy; [b]IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [c]Department of Internal Medicine, Liver Center, Yale University School of Medicine, New Haven, CT, USA; [d]Smilow Cancer Hospital and Liver Cancer Program, New Haven, CT, USA

Keywords
Survival · Benefit · Cirrhosis · Systemic treatment

Abstract

Background: Safety and outcome of atezolizumab/bevacizumab in Child-Pugh B patients with hepatocellular carcinoma (HCC) have not been completely characterized. ***Objectives:*** In this study, we aimed at addressing safety and efficacy of atezolizumab/bevacizumab in Child-Pugh B patients by reviewing the available data and analyzing them by meta-analysis. ***Methods:*** We compared the safety and efficacy of atezolizumab/becavizumab treatment in patients with unresectable HCC and various degrees of liver dysfunction. A total of 8 retrospective, non-randomized, cohort studies were included in this meta-analysis, for a total of 1,071 Child-Pugh A and 225 Child-Pugh B patients. The albumin-bilirubin (ALBI) grade was also used to assess liver function, when available. ***Results:*** Grade ≥3 adverse events were observed in 11.8% of Child-Pugh class A and 26.8% class B patients ($p = 0.0001$), with an odds ratio (OR) of 0.43 (confidence interval [CI] 0.21–0.90; $p = 0.02$). Progression-free survival (PFS) at both 6 months (4.90 ± 2.08 vs. 4.75 ± 2.08 months; $p = 0.0004$) and 12 months (8.83 ± 2.32 vs. 7.26 ± 2.33 months; $p = 0.002$) was lower in Child-Pugh class B patients. A trend toward a higher objective response rate (ORR) was observed in Child-Pugh class A patients (219/856, 25.6%) as compared to Child-Pugh class B patients (25/138, 18.1%; $p = 0.070$), while the probability of obtaining an ORR was significantly greater in Child-Pugh A patients (OR 1.79, CI 1.12–2.86; $p = 0.02$). Median overall survival (OS) was 16.8 ± 2.0 and 6.8 ± 3.2 months in Child-Pugh A and B patients, respectively (mean difference 9.06 months, CI 7.01–11.1, $p < 0.0001$). Lastly, OS was longer in patients with ALBI grades 1–2 than in those with grade 3 (8.3 ± 11.4 vs. 3.3 ± 5.0 months, $p = 0.0008$). ***Conclusions:*** Oncological efficacy of atezolizumab/bevacizumab is moderate in Child-Pugh class B patients, and the shorter PFS and OS associated with the greater likelihood of experiencing treatment-related adverse events observed in these patients suggest great caution and individualization of treatment, possibly with the support of the ALBI grade.

karger@karger.com
www.karger.com/lic

Correspondence to:
Edoardo G. Giannini, egiannini@unige.it

Introduction

About one-third of the patients diagnosed with hepatocellular carcinoma (HCC) present with mildly impaired liver function and this proportion has not changed over the last 2 decades [1]. The global BRIDGE study, including more than 5,000 European and North-American patients with HCC, reported a Child-Pugh class B prevalence of 23–25%. A very recent report based on the Korean Central Cancer Registry identified 2,318 patients with HCC and Child-Pugh class B in a total of 13,838 patients with HCC recorded in the period 2008–2016 and provided survival figures according to the first treatment received [2–4].

In patients with HCC, hepatic decompensation may be present before the tumor is diagnosed or can be precipitated by tumor growth and/or vascular invasion. As preservation of liver function is a critical component when determining treatment options and tolerability, those patients with decompensated disease are often not eligible for various therapies. Whatever the cause of decompensation, patients with HCC who are Child-Pugh class B represent an extremely heterogeneous and difficult-to-treat population for which the survival benefit obtained by the treatment of liver cancer is often hampered by the risk of impending, unresolvable decompensation [5–8].

In patients with unresectable HCC, presence of vascular invasion, extrahepatic spread, or lack of eligibility for locoregional treatment are considered indications for systemic treatment and these characteristics are prevalent among Child-Pugh class B patients with HCC. Indeed, more than half of the Child-Pugh class B patients included in the Korean Primary Liver Cancer Registry were classified as BCLC stage C due to these oncological characteristics, and in these patients, overall survival (OS) with systemic therapy was 3 months [4–9]. Unfortunately, systemic treatment of Child-Pugh class B patients may be challenging, and these patients are usually not included in prospective trials. The only randomized study on this topic failed to demonstrate the efficacy of sorafenib over best supportive care in BCLC C Child-Pugh class B patients, while other studies failed to recruit patients to evaluate its efficacy in this setting [10–12]. Thus, the evidence of a survival advantage of systemic therapy in this clinical setting is lacking and further studies are needed, especially in this era of immunotherapy.

The recent positive results obtained with the use of atezolizumab plus bevacizumab (atezolizumab/bevacizumab) in patients with unresectable HCC and preserved liver function established this combination therapy as the first-line systemic treatment. Since this treatment does not appear to depress liver function, its use in patient within the Child-Pugh B stage and acceptable risk profiles, including those with low bleeding risk, should be explored [13–17]. Unfortunately, the assessment of outcomes in Child-Pugh class B patients with HCC treated with atezolizumab/bevacizumab is limited because available studies remain retrospective in nature with various bias, and therefore, safety and efficacy of atezolizumab/bevacizumab in this setting remains unclear.

Here, we report the result of a meta-analysis of the available studies that assessed the outcomes of treatment with atezolizumab/bevacizumab in patients with unresectable HCC and impaired liver function. Besides providing comprehensive data on safety and efficacy in this understudied population, we also explored whether the use of different modalities of classification of liver dysfunction, using the albumin-bilirubin (ALBI) grade, might improve the selection of patients.

Patients and Methods

The aim of this meta-analysis was to compare the safety and efficacy of atezolizumab/becavizumab treatment in patients with unresectable HCC and various degrees of liver dysfunction. We included studies published in extenso that reported progression-free survival (PFS) and OS data, response rate (i.e., objective response rate [ORR], disease control rate [DCR]), and the presence of adverse events (AEs) when classified according to Common Terminology Criteria for Adverse Events (CTCAE) [18]. The Child-Pugh classification was used to grade the severity of liver dysfunction, and only studies that separately reported the outcomes of Child-Pugh class A and B patients were included in the analyses [2].

Database Search Strategy

This systematic review with meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [19, 20]. We searched using Ovid® (Embase, PubMed, Scopus, and Web of Science), applying search terms referring to atezolizumab/bevacizumab plus HCC plus Child-Pugh: detailed web-search methods can be found in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000533991). Databases were last accessed on March 29, 2023. Publications were screened and selected by two authors (A.P. and F.C.), and duplicate reports were removed.

Data Extraction and Outcome Measures

Data were collected using ad hoc forms (online suppl. Table 2). The following details were extracted: name of the first author, year of publication, total number of patients included in the study, number of patients subdivided according to Child-Pugh class, etiology of liver disease, modality of data collection (i.e., prospective and

retrospective), and main patients' demographic data (e.g., gender, age). As far as AEs are concerned, only AEs with a severity grade ≥3 were considered [18]. When available, data were also analyzed according to various Child-Pugh scores within Child-Pugh class B. The ALBI grade was used, when available, to allow further classification of liver dysfunction into grade 1 (≤−2.60), grade 2 (>−2.60 to ≤−1.39), and grade 3 (>−1.39) [21].

PFS was considered as the time elapsed until radiological evidence of disease progression after atezolizumab/bevacizumab initiation, while OS was defined as the time from atezolizumab/bevacizumab initiation until death for any reason. Response rates were reported according to the Response Evaluation Criteria in Solid Tumors, version 1.0 [22]. ORR (i.e., complete and partial response) as well as DCR (i.e., complete response, partial response, and stable disease) were considered.

The restricted mean survival time was obtained by measuring the area under the Kaplan-Meier curve until a priori established times, which was set at 6 and 12 months. The computation was obtained by integration of parts [23]. The confidence interval (CI) for restricted mean survival times among patients' subgroups was established as previously described [24].

Bias Risk Assessment

The risk of bias in non-randomized intervention studies was evaluated with the risk of bias in non-randomized intervention studies (ROBINS I) tool [25]. The reviewers (A.P. and F.C.) discussed the discrepant results until consensus was reached. Any disagreement was arbitrated and resolved by discussion with a third author (E.G.G.). We checked for publication bias by examining funnel plots and Egger's test [26].

Summary of Data and Statistical Analysis

Continuous data were synthesized and analyzed using mean and standard deviation. Standard deviations of the mean difference were obtained as previously reported [27]. Whereas the outcome measures were reported in median and interquartile range or 95% CI, mean and standard deviation values were estimated using previously described methodology [28].

Odds ratios (ORs) were computed using the Mantel-Haenszel OR method [27]. Age, gender, and liver disease etiology were considered confounding factors, when available. Statistical heterogeneity was reported using I^2 statistics. Random-effects model was used for analysis in the presence of statistical heterogeneity (I^2 >50%), otherwise a fixed-effects model was preferred. Two-sided p values ≤0.05 were considered statistically significant. Data from individual studies were pooled in a meta-analysis using RevMan 5.4.1 (the Cochrane Collaboration, Copenhagen, Denmark).

Results

Studies and Population Characteristics

The sorting process of the publications included in the meta-analysis is reported in online supplementary Figure 1. All the 8 studies included in this meta-analysis were retrospective, non-randomized, cohort analyses, and their general characteristics are reported in Table 1 [14–16, 29–32]. Overall, 1,296 patients were included in this meta-analysis, with 1,071 Child-Pugh A patients and 225 Child-Pugh B patients. Child-Pugh class B patients were further classified into 111 patients with Child-Pugh class B7 and 86 patients with a Child-Pugh class ≥ B8. One study did not report a detailed stratification of Child-Pugh class B patients (n = 25). Mean age was 69.8 years (range 23–96 years), and most patients were males (n = 1,074, 82.3%). The most common etiology of liver disease was nonviral (n = 635, 49.0%), while chronic hepatitis B and chronic hepatitis C accounted for 282/1,196 (23.6%, not available in one study) and 337/1,196 (28.2%, not available in one study) patients, respectively.

Bias Risk Analysis

The detailed bias risks report is shown in online supplementary Table 3. Overall, five of the included studies were at low risk of bias, while 3 were judged to be at moderate risk. No study received a high or critical bias risk judgment. Figure 1a shows the risk of bias summary which reports the authors' judgment about each risk of bias item for each included study, while the risk of bias graph reports the authors' judgment about each risk of bias item across all included studies is shown in Figure 1b.

Safety: Risk of AEs

Four out of 8 studies systematically reported the occurrence of drug-related AEs, including a total of 926 patients. Overall, 128 subjects experienced at least a grade 3 AE, and these events were more frequent in Child-Pugh class B (34/127, 26.8%) than in class A patients (94/799, 11.8%; p = 0.0001).

When data were pooled, there was high heterogeneity and the funnel plot appeared symmetrical with p = 0.745 at Egger's test. Child-Pugh class A patients had a significantly lower risk of experiencing at least a grade 3 AE (OR 0.43, CI 0.21–0.90; p = 0.02, Fig. 2; online suppl. Fig. 2).

Progression-Free Survival

PFS data were available in 6 out of 8 studies, although median PFS had been statistically reached in only four of them. When data were pooled, there was high heterogeneity and the funnel plot appeared symmetric. Child-Pugh class A patients had longer median PFS (8.60 ± 1.48 months) than Child-Pugh class B patients (4.33 ± 1.63 months), resulting in a mean difference of 4.27 months (IC 2.19–6.35; p < 0.0001, Fig. 3a; online suppl. Fig. 3a). Six-month PFS was significantly longer in Child-Pugh

Table 1. Characteristics of the studies included in the meta-analysis

Author, year	Study design	Patients, *n*	Child-Pugh class	
			A (*n*, %)	B (*n*, %)
Cheon et al. [16] (2022)	Retrospective	169	133, 78.7	36, 21.3
De Castro et al. [32] (2022)	Retrospective	147	106, 72.1	41, 27.9
Chuma et al. [29] (2021)	Retrospective	94	81, 86.2	13, 13.8
Sho et al. [30] (2021)	Retrospective	64	60, 93.8	4, 6.2
Himmelsbach et al. [31] (2022)	Retrospective	63	35, 55.6	28, 44.4
Tanaka et al. [15] (2022)	Retrospective	457	427, 93.4	30, 6.6
D'Alessio et al. [14] (2022)	Retrospective	202	154, 76.2	48, 23.8
Jost-Brinkmann et al. [17] (2023)	Retrospective	100	75, 75.0	25, 25.0
All patients		1,296	1,071, 82.6	225, 17.4

class A than in class B patients, with a mean difference of 0.72, IC 0.33–1.12 months (4.90 ± 2.08 vs. 4.75 ± 2.08 months; $p = 0.0004$) (Fig. 3b; online suppl. Fig. 3b), and likewise, 12-month PFS with mean difference of 1.57, IC 0.58–2.56 months (8.83 ± 2.32 vs. 7.26 ± 2.33 months; $p = 0.002$) (Fig. 3c; online suppl. Fig. 3c).

Oncological Response according to Child-Pugh Class

ORR was reported in 5 out of 8 studies for a total of 994 patients. Overall, 244 (24.5%) subjects obtained ORR, with a trend toward higher ORR in Child-Pugh class A patients (219/856, 25.6% vs. Child-Pugh class B, 25/138, 18.1%; $p = 0.070$). The probability of obtaining an ORR was significantly greater in Child-Pugh class A patients (OR 1.79, IC 1.12–2.86, $p = 0.02$, Fig. 4a). When data were pooled, there was low heterogeneity and the funnel plot appeared symmetrical with $p = 0.745$ at Egger's test (online suppl. Fig. 4a).

Six out of 8 studies reported DCR data, including a total of 1,058 patients. DCR was observed in 718/916 (78.4%) Child-Pugh class A patients and in 95/142 (66.9%) Child-Pugh class B patients and this difference was not statistically significant ($p = 0.102$). However, Child-Pugh class A patients had significantly higher probability of DCR compared to Child-Pugh class B patients (OR 1.73, IC 1.17–2.56; $p = 0.006$, Fig. 4b). There was low heterogeneity with a symmetrical funnel plot at bias analysis ($p = 0.615$ at Egger's test) and in pooled analysis (online suppl. Fig. 4b).

Overall Survival

OS figures were available in 5 out of 8 studies, although median OS had been statistically reached only in three of them. Pooled analysis showed high heterogeneity, but the funnel plot appeared symmetrical (online suppl. Fig. 5a).

Weighted mean of median OS was 16.8 ± 2.0 and 6.8 ± 3.2 months in Child-Pugh class A and B patients, respectively. Child-Pugh class A had statistically significant longer median OS than Child-Pugh class B patients (mean difference 9.06 months, CI 7.01–11.1; $p < 0.0001$, Fig. 5a).

The MRST analysis was used as ad hoc survival evaluation to allow the inclusion of all the 5 studies that reported OS. Six-month survival was 5.6 ± 2.9 and 4.6 ± 3.5 months in Child-Pugh class A and B patients, respectively (mean difference 0.88, CI 0.42–1.34 months, $p = 0.0002$, $\chi^2 = 2.57$, I^2 0%) (Fig. 5b; online suppl. Fig. 5b). Likewise, 12-month survival was significantly longer in Child-Pugh class A than in class B patients (10.2 ± 2.9 vs. 7.9 ± 3.5 months, mean difference 2.36, IC 1.36–3.37 months; $p = 0.008$, $\tau^2 = 0.85$, I^2 71%) (Fig. 3c; online suppl. Fig. 5c).

Stratification according to ALBI Grade and Child-Pugh Scores

The ALBI grade was exhaustively reported only in two studies. An ALBI grade 1–2 was observed in a total of 299 patients, including 239 Child-Pugh class A and 60 Child-Pugh class B patients, while ALBI grade 3 included only 17 patients who were all Child-Pugh class B. When data were pooled, there was no evidence of heterogeneity or asymmetry in a funnel plot and OS was significantly longer in patients with an ALBI grade 1–2 (8.3 ± 11.4 months) as compared to those with an ALBI grade 3 (3.3 ± 5.0 months; $p = 0.0008$).

Data allowing to evaluate OS according to various Child-Pugh scores within Child-Pugh class B patients were available in 2 studies alone and allowed only subclassification of patients according to Child-Pugh class B7 ($n = 21$) versus Child-Pugh class ≥ B8 ($n = 45$). When data were pooled, there was no evidence of heterogeneity

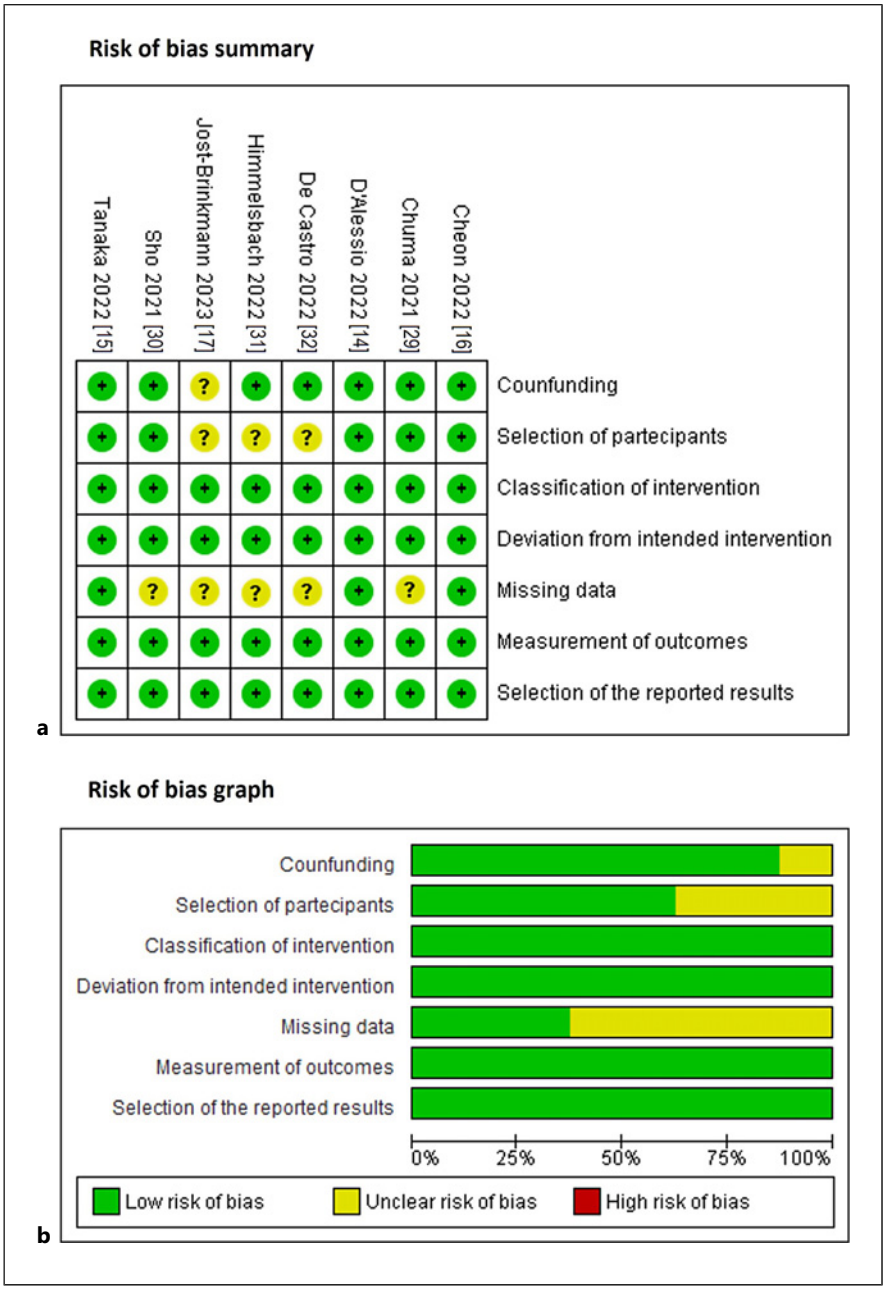

Fig. 1. a Risk of bias summary: review authors' judgment about each risk of bias item for each included study. **b** Risk of bias graph: review authors' judgment about each risk of bias item presented as percentages across all included studies.

or asymmetry in funnel plot and OS was significantly longer in Child-Pugh class B7 patients than in those with class ≥ B8 (3.97 months, IC 1.83–6.10 months; $p = 0.0003$).

Discussion

Child-Pugh B patients with HCC represent a difficult-to-treat population, as curative treatment – ablation, surgery, or transplantation – is hampered by the presence of liver dysfunction, portal hypertension, and by organ shortage, respectively, while chances for locoregional treatment are reduced by the limited residual liver function and concern for precipitating further hepatic decompensation [7, 33]. Systemic therapies are seldom used in these patients due to a greater incidence of AEs and the unclear survival benefit. Additionally, the landmark IMbrave150 trial that demonstrated superior outcomes with atezolizumab/bevacizumab as compared to sorafenib and supported this regimen as new first-line therapy in eligible patients, included only patients with

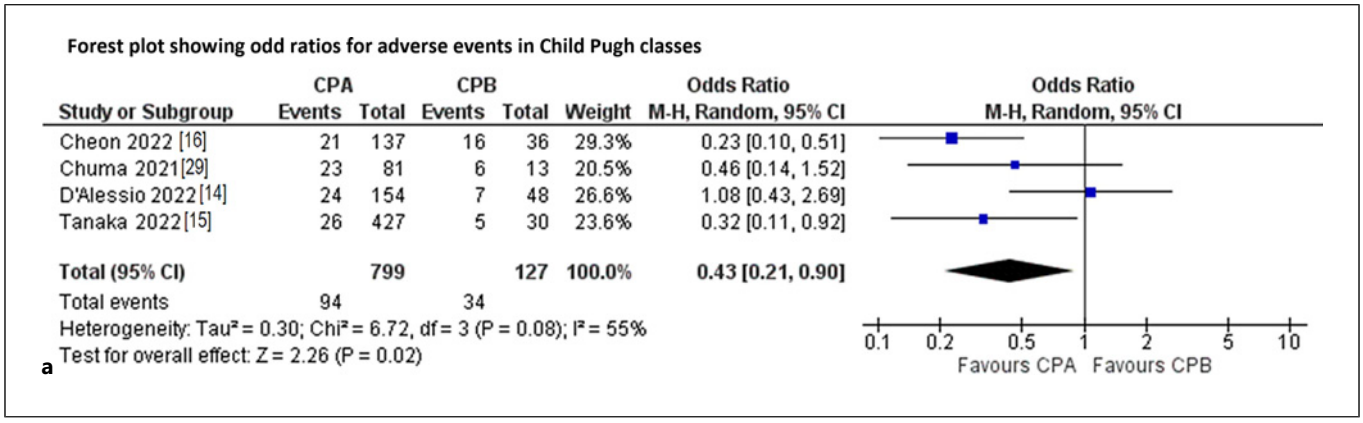

Fig. 2. a Sensitivity analysis of odd ratios for adverse events in Child-Pugh classes. OR, odds ratio.

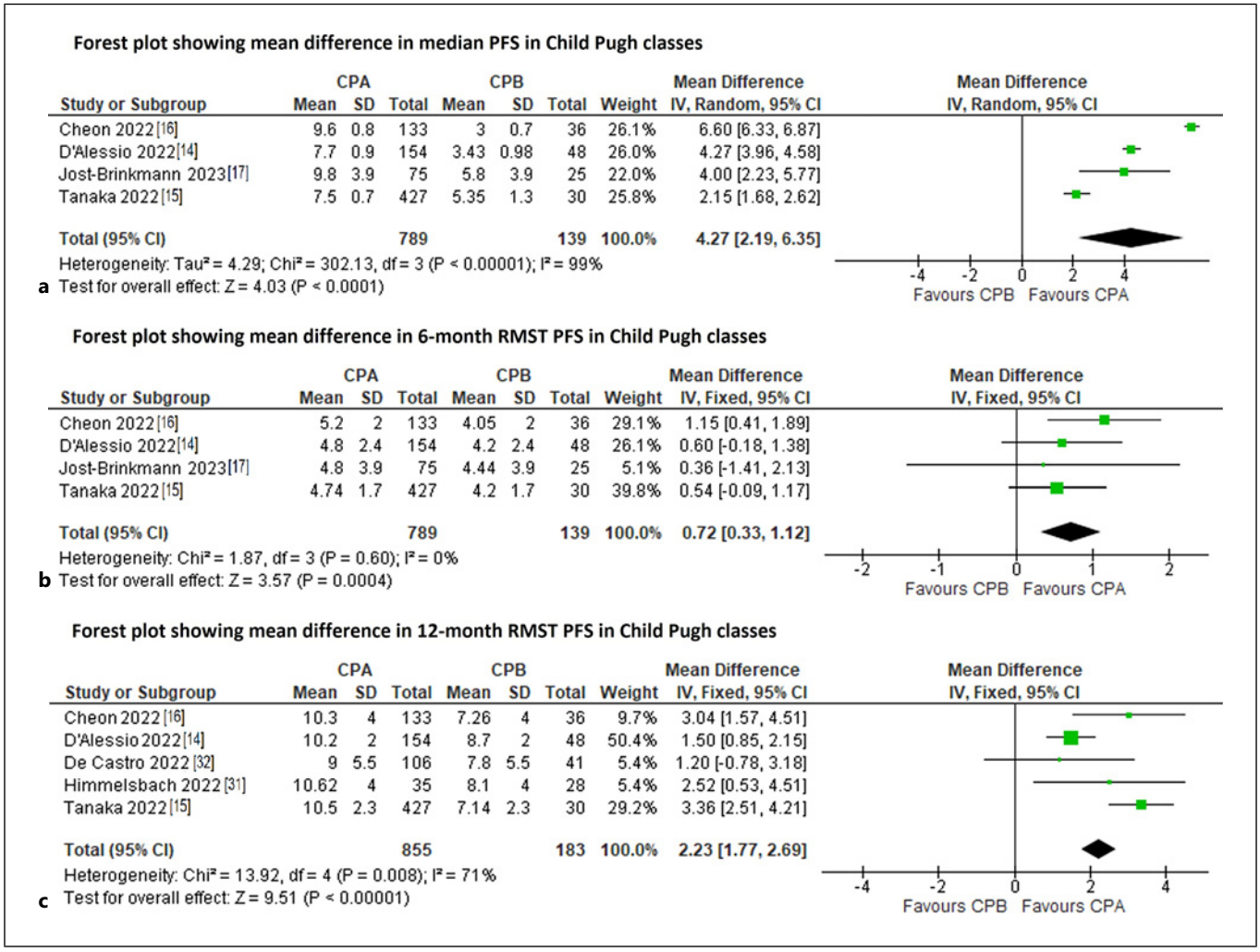

Fig. 3. Forest plots of the sensitivity analysis of (**a**) median, (**b**) 6-month, and (**c**) 12-month progression-free survival (PFS) in Child-Pugh classes.

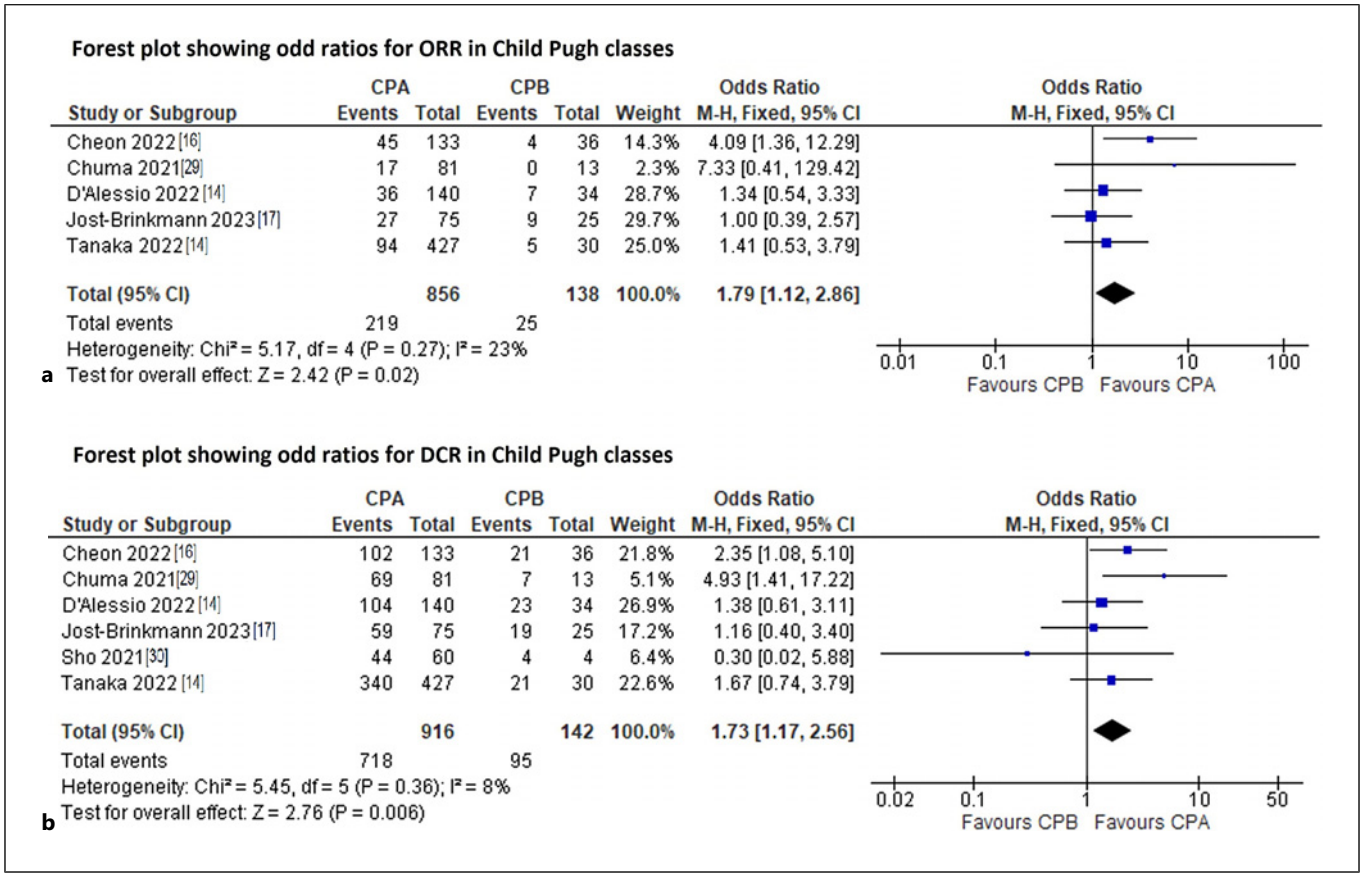

Fig. 4. Sensitivity analysis of OR for (**a**) disease control rate (DCR) and (**b**) objective response rate (ORR) in Child-Pugh classes.

Child-Pugh class A disease, a finding that may raise hesitation for clinical use in patients with decompensated liver disease [13]. In these patients, physicians must adequately weigh the potential survival benefit obtained with oncological treatment against the possible detrimental effect of hepatic decompensation [34, 35]. Thus, when liver transplantation is not a potential treatment option due to inherent limitations or to the presence of extrahepatic spread or macro-vascular invasion, or to the presence of an overall frailty – a finding not adequately captured by the ECOG Performance Status Score – treatment of Child-Pugh class B patients with HCC is often not pursued, and these patients are managed with best supportive care [36–38].

The results of atezolizumab/bevacizumab as systemic treatment for patients with HCC captured the interest of clinicians as the positive effects of this combination could extend to patients with more advanced liver dysfunction with respect to those initially included in the registration trial [13, 34]. In fact, some real-life studies that have included Child-Pugh class B patients showed an OS of approximately 6 months in this group, and although OS was shorter than in Child-Pugh A patients, it was nevertheless longer than the survival figures reported in studies with sorafenib in patients with more decompensated liver disease (i.e., 3–4 months) [5, 10, 39].

This meta-analysis aimed to evaluate the safety and efficacy of atezolizumab/bevacizumab in patients with HCC and impaired liver function and to explore whether the use of additional tools to evaluate liver dysfunction besides the Child-Pugh classification may provide useful information. Overall, we observed that in Child-Pugh class B patients PFS was approximately 4 months shorter as compared to Child-Pugh class A patients, while OS of Child-Pugh class B patients was approximately 7 months, about 9 months less than in Child-Pugh class A patients. Similarly, MRST analysis was used to allow the inclusion of the studies that reported PFS and OS without reaching the median survival, and also these analyses showed that survival figures were influenced by the degree of liver

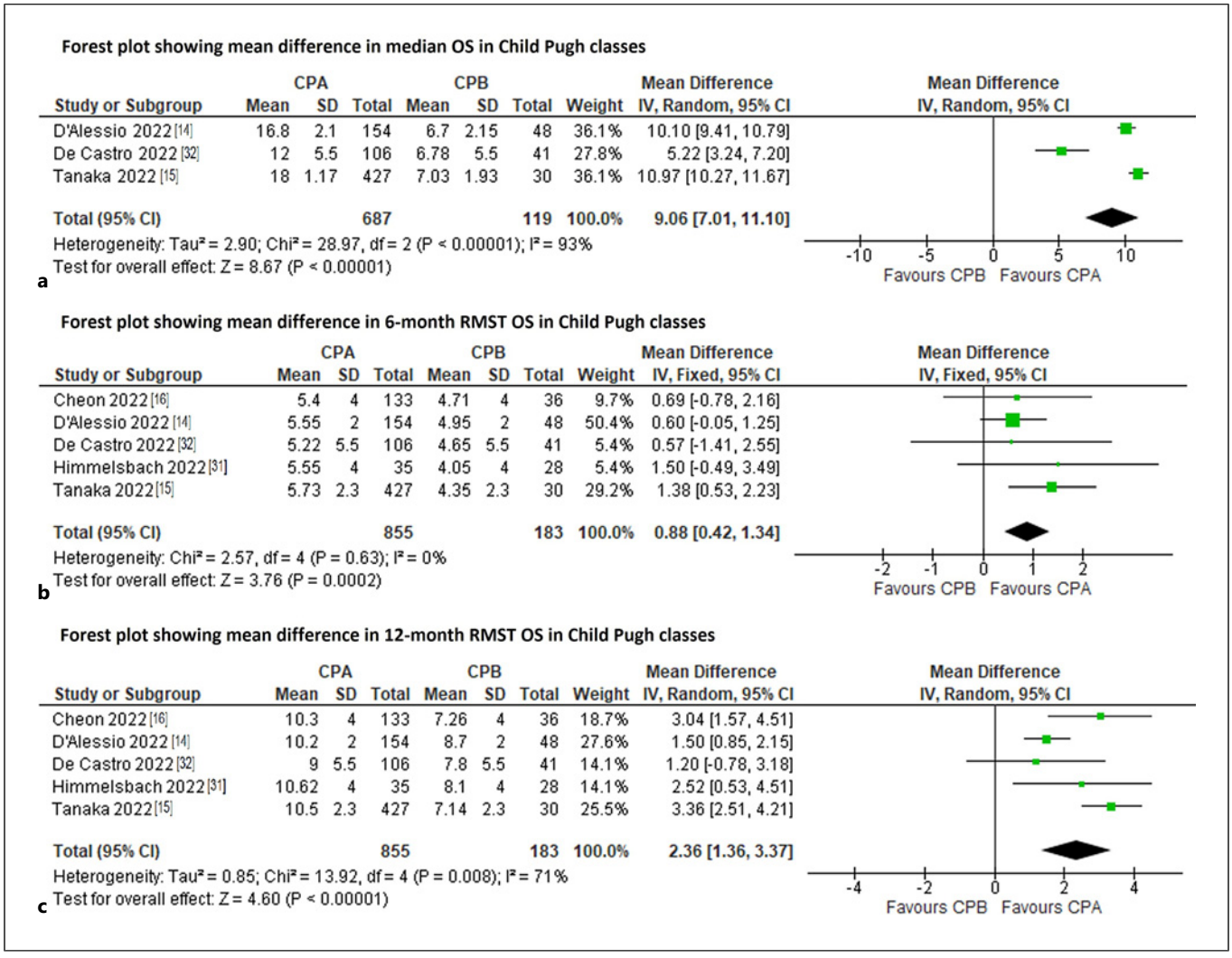

Fig. 5. Forest plots of the sensitivity analysis of (**a**) median, (**b**) 6-month, and (**c**) 12-month overall survival (OS) in Child-Pugh classes.

dysfunction both at 6 and at 12 months. Lastly, despite a greater probability of obtaining both ORR and DCR in Child-Pugh class A patients, the efficacy of oncological treatment was also substantial in Child-Pugh class B patients, with an ORR of 18.1% and a DCR of 66.9%. Albeit lower than those obtained in Child-Pugh class A (ORR 25.6%, DCR 78.4%), these remaining figures may have clinical relevance.

Therefore, it seems that the lower survival outcomes in Child-Pugh class B patients treated with atezolizumab/bevacizumab are only partly related to a reduced oncologic efficacy, and more a consequence of an increased risk of dying due to progression of liver disease or because of non-liver-related deaths. Unfortunately, most studies included in the meta-analysis did not report the causes of death, and thus it was not possible to provide a definite answer to these important clinical questions. It is worth emphasizing that preserving, and possibly improving, liver function is of essence in patients with HCC not only to enhance their likelihood of access to oncological treatments, but also to support their activity by increasing liver disease-related life expectancy [6, 40].

In terms of safety, only half of the studies systematically reported the occurrence of drug-related AEs, and in those studies where these were reported, severe AEs (i.e., at least grade 3) occurred more frequently in Child-Pugh class B (26.8%) than in class A (11.8%) patients, with a 2-fold greater risk of experiencing at least a grade 3 AE in the former group of patients. This may have influenced patient retention, and ultimately

treatment duration, thus negatively influencing survival and oncologic response in Child-Pugh class B patients. Accurate assessment and characterization of AE during atezolizumab/bevacizumab treatment for patients with HCC is of essence as more and more patients will be treated in clinical practice [41, 42]. In this regard, the fact that all the studies available were retrospective, thus with the inherent bias of underreporting of AEs, represents a limitation of this meta-analysis. Furthermore, since most studies did not report the proportion of patients who experienced variceal bleeding, one of the most feared AE in patients treated with atezolizumab/bevacizumab, it is impossible to draw firm conclusions on occurrence rate and the potential limiting role of this (further) decompensating event in Child-Pugh B patients. It must be emphasized that future studies need to stratify patients according to this complication since the presence of varices per se represents an independent prognostic marker of mortality in patients with HCC and would likely be more prevalent in Child-Pugh class B patients given the worsening degree of portal hypertension in this group of patients [43].

Based on the results of the studies available for the use of atezolizumab/bevacizumab in patients with Child-Pugh B disease, it appears that this treatment may be of benefit to some patients whose characteristics cannot be currently identified due to absence of an a priori adequate stratification according to both oncological features/stage and determinants of decompensated liver disease (i.e., biochemical and/or clinical). In this regard, efficacy data on subclassification according to single scores within Child-Pugh class B patients were not available, and 2 studies alone allowed to evaluate OS according to a less stringent subclassification (i.e., B7 vs. ≥ B8), showing that B7 patients had a survival advantage as compared to patients with more advanced liver disease, yet not allowing to perform a subtler analysis regarding causes of death and oncological response. On another note, availability in some studies of the ALBI grade allowed us to assess whether its use could provide a better assessment of patient prognosis in this setting and allow identification of Child-Pugh B patients who may still benefit more from atezolizumab/bevacizumab treatment. Again, the ALBI grade was available in only 2 studies, but our analysis seems to suggest that atezolizumab/bevacizumab treatment could be avoided in patients with an ALBI grade 3, as their median OS was only 3 months, yet due to the small number of patients available, this initial indication needs to be confirmed in larger series.

Our study has several limitations that are inherent to the nature of the published studies available on this topic and included in the meta-analysis. Indeed, all the studies were retrospective, non-randomized, and lacked a control standard of the care group. Although the pooled OS data in patients treated with atezolizumab/bevacizumab was better than the figure reported in studies with sorafenib, a definite message on this important aspect needs to be provided by direct or indirect (e.g., propensity-matched cohorts) comparison with best supportive care. Furthermore, details regarding the oncologic stage and its impact on treatment efficacy were missing in almost all studies, while stratification according to the presence of extrahepatic spread and vascular invasion (if present) is of essence since these characteristics may be the actual drivers of survival [44]. Lastly, details about causes of death are missing, and this does not allow drawing firm conclusions about the actual efficacy of treatment taking into account competitive causes of death in patients with decompensated liver disease.

Data regarding the efficacy and safety outcomes of Child-Pugh class B patients treated with nivolumab are of interest, and in the only available prospective study, Kudo et al. [45] reported an ORR of 12% in a subset of 25 sorafenib-naïve Child-Pugh class B patients treated with nivolumab monotherapy in the CheckMate 40 study, with a median PFS and OS of 3.4 and 9.8 months, respectively, and noteworthy with a safety profile comparable to that observed in patients with Child-Pugh A class within the same study. Although these data are not dissimilar to those obtained in Child-Pugh class B patients treated with atezolizumab/bevacizumab, we feel that in the absence of a direct comparison, it is premature to speculate regarding potential indirect safety and efficacy comparisons between these two regimens in Child-Pugh class B patients.

Notwithstanding these limitations, this meta-analysis indicates that oncological efficacy of atezolizumab/bevacizumab in patients with Child-Pugh class B seems to be preserved, though the shorter survival observed in these patients as compared to patients with less compromised liver function and the increased risk of treatment-related AE suggest caution and individualization of risks. The survival figures observed in Child-Pugh class B patients treated with atezolizumab/bevacizumab are better than those observed in similar patients treated with tyrosine-kinase inhibitors.

In conclusion, this meta-analysis calls for properly designed, prospective, randomized controlled studies that evaluate the efficacy and safety of atezolizumab/bevacizumab in patients whose liver function is not fully preserved. Patients should be properly stratified according to both liver function impairment, using the ALBI grade, and to oncologic stage determinants.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

Edoardo G. Giannini has participated in consulting and/or advisory boards for Roche, AstraZeneca, Eisai, MSD. Mario Strazzabosco is an advisor for ENGITIX.

Author Contributions

Conceptualization: Edoardo G. Giannini, Andrea Pasta, and Francesco Calabrese. Methodology and supervision: Edoardo G. Giannini, Andrea Pasta, Francesco Calabrese, Ariel Jaffe, and Mario Strazzabosco. Validation, visualization, and formal analysis: Andrea Pasta and Francesco Calabrese. Investigation: Andrea Pasta, Francesco Calabrese, Sara Labanca, Simona Marenco, Giulia Pieri, and Maria Corina Plaz Torres. Data curation: Andrea Pasta and Francesco Calabrese. Writing – original draft: Andrea Pasta, Francesco Calabrese, and Edoardo G. Giannini. Writing – review and editing: Ariel Jaffe, Sara Labanca, Simona Marenco, Giulia Pieri, Maria Corina Plaz Torres, Mario Strazzabosco, and Edoardo G. Giannini.

Funding Sources

Mario Strazzabosco gratefully acknowledges the support of the Yale University Liver Center (DK034989 Silvio O. Conte Digestive Diseases Research Core Centers, Clinical Core).

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Garuti F, Neri A, Avanzato F, Gramenzi A, Rampoldi D, Rucci P, et al. The changing scenario of hepatocellular carcinoma in Italy: an update. Liver Int. 2021;41(3):585–97.
2 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646–9.
3 Park J-W, Chen M, Colombo M, Roberts LR, Schwartz M, Chen P-J, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int. 2015;35(9):2155–66.
4 Jeon D, Song G-W, Lee HC, Shim JH. Treatment patterns for hepatocellular carcinoma in patients with Child-Pugh class B and their impact on survival: a Korean nationwide registry study. Liver Int. 2022;42(12):2830–42.
5 Talbot T, D'Alessio A, Pinter M, Balcar L, Scheiner B, Marron TU, et al. Progression patterns and therapeutic sequencing following immune checkpoint inhibition for hepatocellular carcinoma: an international observational study. Liver Int. 2023;43(3):695–707.
6 Cabibbo G, Edeline J. The prognostic role of tumour progression and liver function at progression under immunotherapy for hepatocellular carcinoma. Liver Int. 2023;43(3):528–30.
7 Giannini EG, Savarino V, Risso D, Di Nolfo MA, Del Poggio P, Benvegnù L, et al. Transarterial chemoembolization in Child–Pugh class B patients with hepatocellular carcinoma: between the devil and the deep blue sea. Liver Int. 2010;30(6):923–4; author reply 924-5.
8 Hsu C-Y, Huang Y-H, Su C-W, Lin H-C, Chiang J-H, Lee P-C, et al. Renal failure in patients with hepatocellular carcinoma and ascites undergoing transarterial chemoembolization. Liver Int. 2010;30(1):77–84.
9 Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76(3):681–93.
10 Blanc J-F, Khemissa F, Bronowicki J-P, Monterymard C, Perarnau J-M, Bourgeois V, et al. Phase 2 trial comparing sorafenib, pravastatin, their combination or supportive care in HCC with Child-Pugh B cirrhosis. Hepatol Int. 2021;15(1):93–104.
11 Daniele G, Schettino C, Arenare L, Bilancia D, Farinati F, Federico P, et al. BOOST: a phase 3 trial of sorafenib vs . best supportive care in first line treatment of hepatocellular carcinoma in patients with deteriorated liver function. Hepatoma Res. 2021;7:61.
12 Labeur TA, Achterbergh R, Takkenberg B, Van Delden O, Mathôt R, Klümpen H. Sorafenib for patients with hepatocellular carcinoma and child-pugh B liver cirrhosis: lessons learned from a terminated study. Oncologist. 2020;25:e1274–9.
13 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–905.
14 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;76(4):1000–12.
15 Tanaka T, Hiraoka A, Tada T, Hirooka M, Kariyama K, Tani J, et al. Therapeutic efficacy of atezolizumab plus bevacizumab treatment for unresectable hepatocellular carcinoma in patients with Child-Pugh class A or B liver function in real-world clinical practice. Hepatol Res. 2022;52(9):773–83.
16 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;15:175883592211485.
17 Jost-Brinkmann F, Demir M, Wree A, Luedde T, Loosen SH, Müller T, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma: results from a German real-world cohort. Aliment Pharmacol Ther. 2023;57(11):1313–25.
18 Common Terminology Criteria for adverse events: CTCAE; 2017.
19 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
20 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;74(9):790–9.
21 Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550–8.

22 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 1990 2009;45(2):228–47.
23 Brand L. Advanced calculus: an introduction to classical analysis: Courier Corporation; 2013.
24 Kloecker DE, Davies MJ, Khunti K, Zaccardi F. Uses and limitations of the restricted mean survival time: illustrative examples from cardiovascular outcomes and mortality trials in type 2 diabetes. Ann Intern Med. 2020; 172(8):541–52.
25 Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
26 Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018;74(3): 785–94.
27 Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol. 1992;45(7):769–73.
28 Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
29 Chuma M, Uojima H, Hattori N, Arase Y, Fukushima T, Hirose S, et al. Safety and efficacy of atezolizumab plus bevacizumab in patients with unresectable hepatocellular carcinoma in early clinical practice: a multicenter analysis. Hepatol Res. 2022;52(3):269–80.
30 Sho T, Suda G, Yamamoto Y, Furuya K, Baba M, Ogawa K, et al. Efficacy and effect on liver functional reserve of atezolizumab and bevacizumab for unresectable hepatocellular carcinoma in patients who do not meet eligibility criteria of IMbrave150. Cancers. 2022; 14(16):3938.
31 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. 2022;14(7):1722.
32 de Castro T, Jochheim LS, Bathon M, Welland S, Scheiner B, Shmanko K, et al. Atezolizumab and bevacizumab in patients with advanced hepatocellular carcinoma with impaired liver function and prior systemic therapy: a real-world experience. Ther Adv Med Oncol. 2022;14:17588359221080298.
33 Farinati F, Vanin V, Giacomin A, Pozzan C, Cillo U, Vitale A, et al. BCLC stage B hepatocellular carcinoma and transcatheter arterial chemoembolization: a 20-year survey by the Italian Liver Cancer group. Liver Int. 2015;35(1):223–31.
34 Jaffe A, Taddei TH, Giannini EG, Ilagan-Ying YC, Colombo M, Strazzabosco M. Holistic management of hepatocellular carcinoma: the hepatologist's comprehensive playbook. Liver Int. 2022;42(12):2607–19.
35 Pressiani T, Boni C, Rimassa L, Labianca R, Fagiuoli S, Salvagni S, et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol. 2013;24(2):406–11.
36 Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology. 2015;61(1):184–90.
37 Giannini EG, Bucci L, Garuti F, Brunacci M, Lenzi B, Valente M, et al. Patients with advanced hepatocellular carcinoma need a personalized management: a lesson from clinical practice. Hepatology. 2018;67(5):1784–96.
38 Singh S, Taneja S, Tandon P, Bansal A, Gorsi U, Roy A, et al. A comparison of different frailty scores and impact of frailty on outcome in patients with cirrhosis. J Clin Exp Hepatol. 2022;12(2):398–408.
39 McNamara MG, Slagter AE, Nuttall C, Frizziero M, Pihlak R, Lamarca A, et al. Sorafenib as first-line therapy in patients with advanced Child-Pugh B hepatocellular carcinoma-a meta-analysis. Eur J Cancer. 2018;105:1–9.
40 Cabibbo G, Celsa C, Calvaruso V, Petta S, Cacciola I, Cannavò MR, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol. 2019; 71(2):265–73.
41 Plaz Torres MC, Lai Q, Piscaglia F, Caturelli E, Cabibbo G, Biasini E, et al. Treatment of hepatocellular carcinoma with immune checkpoint inhibitors and applicability of first-line atezolizumab/bevacizumab in a real-life setting. J Clin Med. 2021;10(15): 3201.
42 Stefanini B, Bucci L, Santi V, Reggidori N, Rampoldi D, Lani L, et al. Potential feasibility of atezolizumab-bevacizumab therapy in patients with hepatocellular carcinoma treated with tyrosine-kinase inhibitors. Dig Liver Dis. 2022;54(11): 1563–72.
43 Giannini EG, Risso D, Testa R, Trevisani F, Di Nolfo MA, Del Poggio P, et al. Prevalence and prognostic significance of the presence of esophageal varices in patients with hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2006;4(11):1378–84.
44 Guarino M, Cucchetti A, Pontillo G, Farinati F, Benevento F, Rapaccini GL, et al. Pattern of macrovascular invasion in hepatocellular carcinoma. Eur J Clin Invest. 2021;51(7): e13542.
45. 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; 75(3):600–9.