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Vogel A, Finn RS, Blanchet Zumofen M-H, Heuser C, Sanchez Alvarez J, Leibfried M, Mitchell CR, Batson S, Redhead G, Gaillard VE, Kudo M

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Title:

Atezolizumab in combination with bevacizumab for the management of patients with hepatocellular carcinoma in the first-line setting: systematic literature review and meta-analysis

Authors:

Arndt Vogel[a], Richard S Finn[b], Marie-Hélène Blanchet Zumofen[c], Carolina Heuser[c], Javier Sanchez Alvarez[c], Michael Leibfried[d], Catherine R Mitchell[e], Sarah Batson[e], Gabrielle Redhead[e], Vincent E Gaillard[a], Masatoshi Kudo[f]

Author Affiliations:

[a] Hannover Medical School, Hannover, Germany

[b] Division of Hematology Oncology, Department of Medicine, University of California, Los Angeles, CA, USA

[c] F. Hoffmann-La Roche Ltd, Basel, Switzerland

[d] Genentech Inc., South San Francisco, CA, USA

[e] Mtech Access Limited, Bicester, Oxfordshire, UK

[f]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan

Corresponding author: hepatocellular carcinoma, network meta-analysis, systematic literature review

Arndt Vogel, MD

Medizinische Hochschule Hannover

Carl-Neuberg-Straße 1, 30625 Hannover, Germany

+49 511 5326760

vogel.arndt@mh-hannover.de

Running head:

Atezolizumab-bevacizumab for first-line HCC

Key words: Atezolizumab, Cancer immunotherapy, Hepatocellular carcinoma, Network meta-analysis

Abbreviations

SLR	Systematic literature review
NMA	Network meta-analysis
HCC	Hepatocellular carcinoma
EBM	Evidence-based medicine
CrI	Credible interval
OS	Overall survival
PFS	Progression free survival
HBV	Hepatitis B virus
HCV	Hepatitis C virus
SOC	Standard of care
FDA	Food and Drug Administration
RCT	Randomised controlled trial
PD-L1	Programmed ligand death 1
VEGF	Vascular endothelial growth factor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
AE	Adverse event
RECIST	Response Evaluation Criteria in Solid Tumours
AFP	Alpha-fetoprotein
ECOG PS	Eastern Cooperative Oncology Group Performance Status
BCLC	Barcelona Clinic Liver Cancer
RE	Random effects
HR	Hazard ratio
PVTT	Portal vein tumour thrombosis
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
FE	Fixed effects
IPD	Individual patient data

Abstract

Background:

In 2020, atezolizumab-bevacizumab has become the new standard of care (SOC) for first-line unresectable hepatocellular carcinoma (HCC) patients, following a decade where sorafenib was the preferred first line treatment. In the last few years, a number of novel systemic treatments with non-inferiority and superiority to sorafenib have been approved as first-line treatments.

Objectives:

The objective of this systematic literature review (SLR) and network meta-analysis (NMA) is to compare randomised controlled trial evidence for atezolizumab-bevacizumab with globally relevant pharmacological comparators for first-line treatment of patients with unresectable HCC.

Method:

Randomised controlled trials investigating first-line treatment of HCC in adults with no prior systemic treatment were eligible for inclusion into the SLR and were retrieved from Embase, MEDLINE, and Evidence Based Medicine (EBM) Reviews. Interventions of interest for the NMA included atezolizumab-bevacizumab, sorafenib, lenvatinib, durvalumab (including in combination with tremelimumab), cabozantinib (including in combination with atezolizumab), camrelizumab (including in combination with rivoceranib), pembrolizumab (including in combination with lenvatinib) and tislelizumab. Random effects NMA was conducted for survival endpoints within a Bayesian framework with an informative prior distribution for between study heterogeneity. The hazard ratios for relative treatment effect were estimated with 95% credible intervals (CrIs).

Results:

The SLR identified 49 studies, of which eight formed a connected evidence network permitting the indirect treatment comparison of atezolizumab-bevacizumab with comparators of interest. The indirect comparisons suggested an improved overall survival (OS) with atezolizumab-bevacizumab versus most comparators. All indirect treatment comparison results for atezolizumab-bevacizumab included the null value within the 95% CrI (n=1) for OS and progression free survival (PFS).

Conclusions:

The results of the NMA indicate atezolizumab-bevacizumab is associated with superior or comparable OS and PFS together with a manageable safety profile compared with globally relevant comparators in the unresected HCC indication. The findings support that atezolizumab-bevacizumab remains SOC for the management of first-line unresectable HCC patients.

Key Points:

An SLR and a NMA were conducted to compare RCT evidence for atezolizumab-bevacizumab with comparators for first-line unresectable HCC.

The SLR identified 49 studies, of which eight formed a connected evidence network to permit the indirect treatment comparison of atezolizumab-bevacizumab with cabozantinib (± atezolizumab), camrelizumab + rivoceranib, durvalumab (± tremelimumab), lenvatinib, pembrolizumab + lenvatinib, and tislelizumab.

The results of the NMA indicate atezolizumab-bevacizumab is associated with superior or comparable (camrelizumab-rivoceranib) OS together with a manageable safety profile compared with globally relevant treatments.

The findings support that atezolizumab-bevacizumab should remain standard of care for the management of first-line unresectable HCC patients.

Introduction

Hepatocellular carcinoma (HCC) accounts for 75–90% of all primary liver cancer cases and is the third leading cause of cancer-related mortality worldwide [1-3]. In approximately 70–90% of cases, HCC occurs in patients with chronic liver disease and cirrhosis; hence, the major risk factors for HCC are chronic infection with hepatitis B and C viruses (HBV, HCV), excessive alcohol intake, obesity, type 2 diabetes, and smoking [1].

Prior to the introduction of new systemic therapies, sorafenib provided the only first-line systemic pharmacological treatment and was the standard of care (SOC) for unresectable HCC [4]. The oral multi-kinase inhibitor sorafenib was first licensed by the food and drug administration (FDA) in 2007 [5], offering a statistically significant improvement in overall survival (OS) compared with placebo, with a median survival of 10.7 months [6].

Since 2017, new systemic therapies for advanced HCC are available, resulting in a major paradigm shift in the treatment pathway [4]. Lenvatinib was approved by the FDA as a first-line treatment for unresectable HCC in 2018, as the Phase 3 randomised controlled trial (RCT) (REFLECT: NCT01761266) showed median OS non-inferiority compared with sorafenib [7].

In a Phase 3 RCT evaluating the efficacy and safety of the combination regimen in patients with unresectable HCC (IMbrave150: NCT03434379), atezolizumab-bevacizumab showed clinically meaningful improvements to OS and progression-free survival (PFS) compared with sorafenib, which has led to current approval globally [8]. Atezolizumab-bevacizumab received approval by the FDA in 2020 and is now considered the SOC for first-line systemic therapy of unresectable HCC [5, 9-11]. Atezolizumab is a monoclonal antibody that binds to anti-programmed ligand death-1 (PD-L1) and prevents the interaction between PD-L1 and its receptors [12, 13]. Bevacizumab is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody that targets VEGF to inhibit angiogenesis and tumour growth [14, 15].

While atezolizumab-bevacizumab is the preferred first line treatment in many countries [8, 11, 16], a number of novel systemic treatments with non-inferiority to sorafenib have been approved as first-line treatments [16]. In Europe, sorafenib or lenvatinib are recommended as alternative first-line treatments [11]. Most recently, durvalumab in combination with tremelimumab was also approved by the FDA (October 2022) and recommended for approval by the European Medicines Agency (January 2023) for the treatment of unresectable HCC, following Phase 3 trial results (HIMALAYA: NCT03298451) identifying superiority compared with sorafenib, with a favourable safety profile [17].

The objective of this systematic literature review (SLR) and network meta-analysis (NMA) is to compare RCT evidence for atezolizumab-bevacizumab with globally relevant pharmacological comparators for first-line treatment of patients with unresectable HCC.

Methods

Search strategy and selection criteria

An SLR was conducted to identify RCTs studying first-line treatment with systemic therapies for unresectable HCC in adults with no prior systemic treatment history. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the PRISMA-P and PRISMA-NMA extension guidelines. Interventions of interest for the SLR included combination atezolizumab-bevacizumab, durvalumab (including in combination with tremelimumab), cabozantinib (including in combination with atezolizumab), camrelizumab (including in combination with rivoceranib, previously known as apatinib), lenvatinib, pembrolizumab (including in combination with lenvatinib), and sorafenib. Locoregional modalities were excluded. Eligible studies reported at least one outcome of interest: OS, PFS, or adverse events (AEs). Included studies were Phase 3 RCTs published in English that met the inclusion criteria described above.

Publication records were retrieved from Embase, MEDLINE, and Evidence Based Medicine (EBM) Reviews. Database searches were originally performed in May 2019, with updates conducted in March 2020 and September 2022 (Table S1 [Supporting Information]). The database searches were supplemented by a hand search of scientific conferences, health technology assessment reports, clinical trial registries, and reference lists from included publications and relevant SLRs (Table S2 [Supporting Information]).

Records were screened by title and abstract, followed by full-text review by two independent reviewers, with discrepancies resolved through discussion or through intervention of a third reviewer.

Source data analysis

Data were extracted by an analyst and checked by a second analyst. Two independent reviewers assessed the risk of bias (with discrepancies adjudicated by a third advisor) based on guidance from the Centre for Reviews and Dissemination [18].

The feasibility of conducting indirect comparisons of Phase 3 trials investigating comparators with study data from multiple countries and approved/anticipated approval globally further referred as globally relevant for first-line HCC was examined. Interventions of interest for the NMA were aligned with those of interest for the SLR in addition to tislelizumab. Tislelizumab was not approved at the time of the most recent database search but RATIONALE-301 data were identified in the SLR on the basis of the sorafenib treatment arm [19]. Outcomes of interest for the indirect comparisons included OS and PFS as time-to-event endpoints. Assessment of heterogeneity in the evidence network included qualitative assessment of study designs, outcome measures, and patient populations. Studies reporting PFS according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 response criteria by blinded independent review facility (as aligned with IMbrave150) were considered for inclusion. Subgroup analyses were conducted to investigate patient characteristics possibly affecting the treatment outcomes when imbalances were observed in the distribution of factors. Subgroup analyses were conducted to examine population differences in region, aetiology, alpha-fetoprotein (AFP), Eastern Cooperative Oncology Group performance status (ECOG PS) and Barcelona Clinic Liver Cancer (BCLC) status, where feasible.

Descriptive summary statistics were used to compare patient characteristics and safety outcomes. Indirect comparisons of treatment effects for the time-to-event endpoints (OS and PFS) were analysed using a generalised linear model with random effects (RE) within a Bayesian framework, which required the assumption of proportional hazards to be upheld. However the assessment of proportional hazards was not formally conducted across the studies as the outlined approach to analysis is consistent with other published analyses in this area [20-23]. The traditional RE approach imprecisely estimates between-study heterogeneity when few studies are available for meta-analysis [24]. Therefore, informative priors were used for the heterogeneity of treatment effects across trials, given the limited number of studies available to inform each pairwise comparison in the Bayesian RE approach [25]. Hazard ratios (HRs) with 95% credible intervals (CrIs) and Bayesian posterior probability estimates of atezolizumab-bevacizumab being superior to the other treatments were calculated for each indirect comparison [26]. An improved

benefit of atezolizumab-bevacizumab over comparators was inferred in instances where a HR is less than 0.9 and an improved benefit of the comparators was inferred in instances where a HR is greater than 1.1. By using informative priors for the heterogeneity of treatment effects across trials, CrIs are also affected by prior belief on the between-trial heterogeneity, instead of relying solely on the trials in the network to calculate the heterogeneity. This can impact the width of the intervals when comparing Bayesian and frequentist frameworks. All analyses were conducted using R version 3.4.2 and WinBUGs; specifically, the R2WinBUGS package was used [27].

Results

The most recent database search, conducted on 15th September 2022, identified 2,113 records; 74 underwent full text review, and 41 were included. A further eight records were identified by handsearching, and 64 records were included based on the previous searches, conducted in May 2019 and March 2020. The SLR included a total of 113 publications reporting on 49 unique studies (Figure 1).

The evidence network comprised eight studies identified in the SLR that investigated globally relevant treatments that were able to connect within a network containing IMbrave150 (Figure S1 [Supporting Information]): CheckMate 459 [28], COSMIC-312 [29], HIMALAYA [17], IMbrave150 [30], LEAP-002 [31], NCT03764293 [32], RATIONALE-301 [19], and REFLECT [7]. The remaining 41 unique studies in the SLR were unable to connect within the evidence network due to the studies investigating non relevant comparators.

Assessment of the studies in the evidence network demonstrated inter-study variability in the study designs and populations (Table S3 and S4 [Supporting Information]). Where reported, median follow-up was shorter with CheckMate 459 (15.2 and 13.4 months in the nivolumab and sorafenib arms, respectively), COSMIC-312 (13.3 months), IMbrave150 (15.6 months) and NCT03764293 (14.5 months) compared with the other studies in the network such as LEAP-002 (32.1 months), HIMALAYA (32.2-33.1 months) and REFLECT (27.7 months). NCT03764293 included patients that were younger in age (median 58 and 56 years in the combination and sorafenib arms, respectively) compared with the other studies in the network (median age range 60–67 years). COSMIC-312 included a smaller proportion of patients with BCLC C (65-68%) compared with the other studies in the network (range 76–86%). NCT03764293 and RATIONALE-301 included a larger proportion of patients with ECOG PS 1 (range 46–57%) compared with the other studies in the network (range 27%–39%). CheckMate 459, COSMIC-312, and HIMALAYA included a smaller proportion of patients with HBV (range 29–31%) compared with the other studies in the network (range 42–77%). The proportion of patients enrolled from the Asia-Pacific region varied across studies, with three studies including a majority of patients from this region; RATIONALE-301 (63%), REFLECT (67%) and NCT03764293 (83%), The remaining studies included 25–43% of patients from Asia-Pacific regions. IMbrave150 included 73/501 (15%) of patients with a tumour thrombus in the main trunk and/or contralateral portal vein (PVTT stage Vp4), who are nearly always excluded from pivotal HCC trials (HIMALAYA, LEAP-002, RATIONALE-301, REFLECT) due to their poor prognosis [33]. Thus, a non-Vp4 data set from IMbrave150 was included in the base case analyses (and the full IMbrave150 data set is considered in a sensitivity analysis).

All trials in the network reported HRs for OS and PFS but the assessment of proportional hazards was not formally conducted. Tumour response for PFS was assessed using RECIST v1.1 criteria by blinded independent central review in seven of the eight studies. HIMALAYA reported PFS by investigator assessment only (not blinded independent central review) but was included in the analyses to permit indirect treatment comparisons with durvalumab (± tremelimumab).

While REFLECT reported PFS using RECIST v1.1 criteria by blinded independent central review for the total population, it only reported subgroup analyses of PFS using the modified RECIST (mRECIST) criteria by investigator assessment, and thus REFLECT was excluded from analyses exploring subgroups.

The risk of bias was generally low across the five trials that were reported as full publications, and risk of bias could not be assessed for LEAP-002, NCT03764293, and RATIONALE-301, which were reported as conference presentations only at this time. Lack of study blinding was the greatest concern for all included studies except LEAP-002, which was double-blinded.

OS is the most objective endpoint when comparing results from different trials and was the primary or co-primary endpoint for all studies. In the OS network, indirect treatment comparisons suggested improved OS benefit with atezolizumab-bevacizumab versus cabozantinib-atezolizumab (HR 0.75 [95% CrI 0.38, 1.48]; with 83% Bayesian posterior probability of being superior), durvalumab (0.79 [95% CrI 0.41, 1.49]; 81%), durvalumab-tremelimumab (0.87 [95% CrI 0.45, 1.66]; 70%), lenvatinib (0.74 [95% CrI 0.39, 1.40]; 87%), lenvatinib-pembrolizumab (0.88 [95% CrI

0.40, 1.49]; 67%), nivolumab (0.80 [95% CrI 0.42, 1.49]; 81%), and tislelizumab (0.80 [95% CrI 0.42, 1.52]; 80%), and no difference against camrelizumab-rivoceranib (1.09 [95% CrI 0.56, 2.14]; 37%; Table 1).

Findings from an OS sensitivity analysis including all patients in IMbrave150 (i.e. including Vp4 patients) were consistent with the base-case analysis, with only minor changes in the point estimates (in favour of atezolizumab-bevacizumab) (Table S5 [Supporting Information]). Subgroup analyses were conducted to examine population differences in region, aetiology, AFP, ECOG PS and BCLC status (Table S5 [Supporting Information]). The OS benefit was more robust with atezolizumab-bevacizumab than the comparators in the HBV and HCV analyses and more robust with atezolizumab-bevacizumab than the available comparators in the AFP<400 ng/ml analyses. Across the remaining subgroups explored, the results were similar with the base-case, with the exception of those versus camrelizumab-rivoceranib; the OS benefit was more robust with atezolizumab-bevacizumab than camrelizumab-rivoceranib in the Asia-Pacific region, in patients with ECOG PS 1, and in patients with BCLC B.

Indirect comparisons of PFS suggested improved benefit with atezolizumab-bevacizumab versus durvalumab (0.65 [95% CrI 0.17, 2.29]; 87%), durvalumab-tremelimumab (0.73 [95% CrI 0.20, 2.57]; 81%), nivolumab (0.71 [95% CrI 0.19, 2.55]; 83%), and tislelizumab (0.59 [95% CrI 0.16, 2.10]; 89%). There was also evidence of a potential improved benefit of the comparators camrelizumab-rivoceranib (1.26 [95% CrI 0.34, 4.60]; 26%) and lenvatinib-pembrolizumab (1.22 [95% CrI 0.24, 5.74]; 32%). However, there was no evidence of an improved benefit of PFS with atezolizumab-bevacizumab versus cabozantinib (0.93 [95% CrI 0.24, 3.44]; 58%), cabozantinib-atezolizumab (1.05 [95% CrI 0.29, 3.88]; 45%), and lenvatinib (1.01 [95% CrI 0.27, 3.63]; 48%).

Findings from a PFS sensitivity analysis including all patients in IMbrave150 (i.e. including Vp4 patients) were consistent with the base-case analysis with only minor changes in the point estimates (in favour of atezolizumab-bevacizumab) (Table S6 [Supporting Information]). Limited comparator data were available for subgroup analyses of PFS (Table S6 [Supporting Information]). The PFS benefit was more robust with atezolizumab-bevacizumab than cabozantinib-atezolizumab in the Asia-Pacific region and non-viral patients. The PFS benefit was more robust with atezolizumab-bevacizumab than camrelizumab-rivoceranib in the Asia-Pacific region, in patients with HBV, and AFP<400 ng/ml. Across the remaining subgroups explored the results were similar to the base-case.

The comparative assessment of AEs was performed qualitatively. Occurrence of all-grade treatment related AEs (TRAEs) was higher with sorafenib, cabozantinib ± atezolizumab, lenvatinib ± pembrolizumab, and camrelizumab-rivoceranib compared with atezolizumab-bevacizumab (Table 2). Fewer TRAEs were reported with durvalumab ± tremelimumab, nivolumab, and tislelizumab compared with atezolizumab-bevacizumab. Patients receiving atezolizumab-bevacizumab experienced more all-grade treatment related serious AEs (TRSAEs) and more treatment discontinuation due to AEs than patients receiving any of the other comparators, except camrelizumab-rivoceranib, although it is noted the sorafenib-treated patients in IMbrave150 generally had a higher rate of all-grade TRSAEs and treatment discontinuations due to AEs than the sorafenib-treated patients in the comparator trials.

Discussion

This NMA compared globally relevant therapies in first-line treatment of patients with locally advanced or metastatic unresectable HCC and no prior systemic treatment history. The analysis was based on RCT evidence identified by an SLR, which permitted a series of robust indirect treatment comparisons. Results of the NMA demonstrated superior or comparable OS and PFS with atezolizumab-bevacizumab versus available comparators of interest.

All trials included in the network featured an open-label design, except LEAP-002 which may have influenced duration of treatment of the control arms (sorafenib) in other studies and safety endpoints. Inclusion of the HIMALAYA trial in the NMA of PFS (which reported investigator assessed PFS only) was permitted to enable comparison of durvalumab and durvalumab-tremelimumab. IMbrave150 included a higher-risk population (including patients with PVTT stage Vp4) compared with the comparator trials while still meeting its primary endpoints [8].

In indirect comparisons, OS offers the most objective assessment of clinical efficacy. In this analysis, clinical efficacy results remained largely consistent with primary findings when analysed by sensitivity analyses (including Vp4 patients in the IMbrave150 dataset) and when analysed in subgroups of patients based on geographic region, aetiology, AFP, ECOG PS, and BCLC status. The OS benefit was more robust with atezolizumab-bevacizumab than the comparators in the HBV and HCV analyses and the available comparators in the AFP<400 ng/ml analyses. Furthermore, the OS benefit was more robust with atezolizumab-bevacizumab than camrelizumab-rivoceranib in the Asia-Pacific region, in patients with ECOG PS 1, and in patients with BCLC B. Across the remaining subgroups explored the results were similar to the base-case with no additional benefit observed of atezolizumab-bevacizumab against camrelizumab-rivoceranib. Notably, the study investigating camrelizumab-rivoceranib (NCT03764293) was identified as a potential outlier in terms of age, BCLC status, ECOG PS, aetiology, and region; these patient characteristics suggest the study may not be fully appropriate for the indirect comparison and potentially residual differences in characteristics could have a prognostic impact on treatment effect that would bias the indirect comparison. It is important to highlight that the RE model accounts for additional uncertainty due to the between-study heterogeneity in the network. Hence, the NMA estimates for indirect comparisons have CrIs broader than the confidence intervals reported in head-to-head studies; for the comparison of atezolizumab-bevacizumab with sorafenib, the OS estimate from the direct comparison in the base-case population was 0.68 (95% confidence interval: 0.51, 0.89).

Due to differences in the definitions of endpoints, inclusion and exclusion criteria, follow-up time, and duration of treatment across trials and treatment arms (e.g. deaths due to AEs and treatment discontinuations), meta-analysis of safety outcomes can be challenging. While comparison of reported AE occurrences were included, detailed comparisons of toxicity profiles were not feasible in this NMA. As such, the absolute safety numbers should be interpreted in the context of the differential impact of AEs on patients' lives and the differences in the follow-up time and treatment durations across trials and treatment arms. Issues with toxicity of sorafenib and lenvatinib have been well documented [34-36]. Atezolizumab-bevacizumab provides a different AE profile, reflected in the delayed time to deterioration of quality of life compared with sorafenib [8]. Further, immune-related AEs are a characterised risk with regimens using a cancer immunotherapy component [37].

A robust evidence network of trials was incorporated into this NMA. The indirect comparisons showed more favourable OS and PFS results for the anti-PD-L1 and anti-VEGF combination atezolizumab-bevacizumab compared with most single or double-agent targeted systemic treatments.

Whilst the indirect comparisons provide evidence of a potential improved PFS benefit of the comparators camrelizumab-rivoceranib and lenvatinib-pembrolizumab, the study investigating camrelizumab-rivoceranib (NCT03764293) was identified as a potential outlier in terms of population and the indirect comparison with lenvatinib-pembrolizumab is based on three studies in the chain of evidence with two common comparators (IMbrave150/REFLECT/LEAP-002) which increases the risk of bias and uncertainty in the estimate.

More frequent reporting of all-grade TRSAEs and AEs leading to treatment discontinuation was observed in IMbrave150 for atezolizumab-bevacizumab compared with the other studies, with the exception of camrelizumab-

rivoceranib [32]. However, the overall effect of each treatment from a patient's perspective is not captured in a qualitative comparison of the occurrence of AEs.

The results of the current NMA are broadly consistent in terms of direction of treatment effect with those from previously conducted NMAs in first-line HCC [20-22, 38, 23]. However, some differences can be observed in the methodology. The two most recently published NMAs from Fong et al and Fulgenzi et al were conducted using a frequentist approach with a RE [38] or fixed-effect (FE) [23] model, respectively and a comparison of the results of these analyses with the current analysis is presented in Table S7 (Supporting Information). The current analysis was conducted using a Bayesian approach that accounted for study heterogeneity by employing a RE model with an informative prior distribution for between study heterogeneity. Moreover, Fong et al generated pseudo individual patient data (IPD) from study reported KM curves and pooled these data for atezolizumab-bevacizumab and sintilimab-bevacizumab, to generate a common arm for analysis which 'combined anti-programmed-death and anti-VEGF pathway inhibitor monoclonal antibodies'; IPD were reconstructed and a HR generated for input in the NMA [38]. No other treatments were pooled into treatment nodes within the network presented by Fong et al, thus indirect comparisons of atezolizumab-bevacizumab with the remaining comparators were not presented [38]. The results presented by Fong et al for the comparison of combined anti-programmed-death and anti-VEGF pathway inhibitor monoclonal antibodies treatment (i.e for atezolizumab-bevacizumab and sintilimab-bevacizumab biosimilar) with other comparators included in the current analyses are similar in terms of point estimates and direction of treatment effect for OS but there are differences noted for the comparison with cabozantinib + atezolizumab and lenvatinib for PFS (Table S7 [Supporting Information]). This is a consequence of the inclusion of data from ORIENT-32 [39] in the pooled atezolizumab-bevacizumab and sintilimab-bevacizumab data set, thus the results are not directly comparable with the current analysis [38]. The results presented by Fulgenzi at al are aligned with the current analysis in terms of point estimates and direction of treatment effect for both OS and PFS, although the analysis by Fulgenzi et al does not include camrelizumab-rivoceranib, lenvatinib-pembrolizumab and tislelizumab as comparators (Table S7 [Supporting Information]) [23]. Notably across both published analyses the estimates of uncertainty (i.e 95% CIs) are smaller in comparison with the current analysis (95% CrI). In Fulgenzi et al, this is a consequence of conducting a FE model (i.e the estimates therefore do not account for between study heterogeneity and report narrower 95% CIs versus estimates form a RE model) [23]. In Fong et al, this is dependent on the fact of combining data across two studies for the intervention treatment (i.e combined atezolizumab-bevacizumab and sintilimab-bevacizumab biosimilar) and so the data set for the intervention is larger and therefore the indirect treatment comparisons are associated with less uncertainty [39].

The authors of the Fulgenzi et al NMA stated heterogeneity in the data sets in terms of patients with PVTT stage Vp4 [23], which was not highlighted by Fong et al [38], but neither analysis addressed this heterogeneity in their analyses. In comparison the current NMA excludes patients with PVTT stage Vp4 from the IMbrave150 data set to align with the lower-risk comparator study populations more closely and a comprehensive exploration of multiple subgroup analyses was conducted for both outcomes. In addition, Fong et al and Fulgenzi et al included different comparators. The current analysis focused on systemic therapies, therefore locoregional therapies (such as selective internal radiotherapy, transarterial chemoembolisation) were not considered. Due to the earlier search dates, Fong et al could not identify data for three comparators of interest for the current analysis (LEAP-002, NCT03764293 RATIONALE-301) [38]. While Fulgenzi et al used a broader set of comparators, the current analysis focused on newly globally relevant comparators for first-line treatment of unresectable HCC [38, 23].

This analysis should be interpreted with consideration of certain limitations. The indirect comparisons would be more robust if access to full study reports and patient-level data were available, particularly for the subgroup analyses that were not reported consistently across trials. As with all NMAs, this analysis assumes a similar distribution of effect modifiers in the evidence network. An imbalance of factors may lead to a biased estimation of relative effects. Whilst heterogeneity across the studies has been explored, this was limited for some comparators due to limited reporting of subgroup data. The current NMA included globally relevant comparators. Notably, first-line therapies tested and approved in China only were excluded from the current analysis (including sintilimab-IBI305 and donafenib) [16].

Due to the recent emergence of a number of novel systemic therapies for the treatment of unresectable HCC, variation in treatment pathways and follow-up may impact OS results. The development and implementation of second-line therapies for unresectable HCC also present a limitation [40]. Consequently, evolution of second-line systemic therapies and cancer immunotherapies in later lines may have impacted the OS in some studies. As a result, further research should continue to assess the efficacy of treatment pathways in patients with unresectable HCC. In addition, emerging adjuvant therapies in HCC might impact the overall patient journey and treatment algorithms in the near-to-mid-term future.

Conclusion

The results of the current NMA indicate that combination treatment with atezolizumab-bevacizumab is associated with superior or comparable OS and PFS together with a manageable safety profile compared with globally relevant options in the unresectable HCC indication. The findings support that atezolizumab-bevacizumab remains the standard of care for the management of first-line unresectable HCC patients [5, 9-11].

Statement of Ethics:

This study is based exclusively on published literature. An ethics statement is therefore not applicable.

Conflict of interest statement:

Arndt Vogel had been directly paid honoraria and has been paid consulting or advisory roles for AstraZeneca, Beigene, Böhringer Mannheim, BMS, BTG, EISAI, GSK, Inycte, Ipsen, MSD, Hoffmann-La Roche, Servier, Sirtex, and Tahio.

Richard Finn has been paid consulting/advisory roles for AstraZeneca, Bayer, BristolMyersSquibb, Eisai, Exelixis, Eli Lilly, Merck, Hoffmann-La Roche, Gennetech, Cstone, and Hengrui. His institution has conducted research for Bayer, BristolMyersSquibb, Eisai, Eli Lilly, Merck, Pfizer, Hoffmann-La Roche, and Genentech. Dr. Finn has participated in speakers' bureau for Genentech.

Masatoshi Kudo had been directly paid honoraria by Eisai, Chugai, Eli Lilly, Takeda, and Bayer. His institution has conducted research for Otsuka, Chugai, GE Healthcare, Taiho, AbbVie, EA Pharma, and Eisai.

Marie-Helene Blanchet Zumofen, Carolina Heuser, Javier Sanchez Alvarez, and Vincent E. Gaillard are currently or have been during the past 2 years employed by Hoffmann-La Roche Ltd. Michael Leibfried is employed by Genentech Inc. Marie-Helene Blanchet Zumofen, Carolina Heuser, Javier Sanchez Alvarez, Vincent E. Gaillard and Michael Leibfried own stocks (currently or in the past 2 years) in Hoffmann-La Roche Ltd.

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Author Contributions:

Arndt Vogel, Richard Finn, Marie-Helene Blanchet Zumofen, Carolina Heuser, Javier Sanchez Alvarez, Michael Leibfried, Catherine R. Mitchell, Sarah Batson, Gabrielle Redhead, Vincent E. Gaillard and Masatoshi Kudo contributed to the design and interpretation of findings. Catherine R. Mitchell, Sarah Batson, Gabrielle Redhead conducted the

systematic review and statistical analyses. Sarah Batson wrote the first draft of the report with input from Arndt Vogel, Richard Finn, Marie-Helene Blanchet Zumofen, Carolina Heuser, Javier Sanchez Alvarez, Michael Leibfried, Catherine R. Mitchell, Gabrielle Redhead, Vincent E. Gaillard and Masatoshi Kudo. All authors participated in the writing and editing of the manuscript, and confirm they had full access to all the data in the study and accept responsibility to submit for publication.

Data Availability Statement:

This manuscript makes use of publicly available data from published studies. All data generated during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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Figure 1: PRISMA flow diagram

Abbreviations: EBMR, evidence-based medicine reviews; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

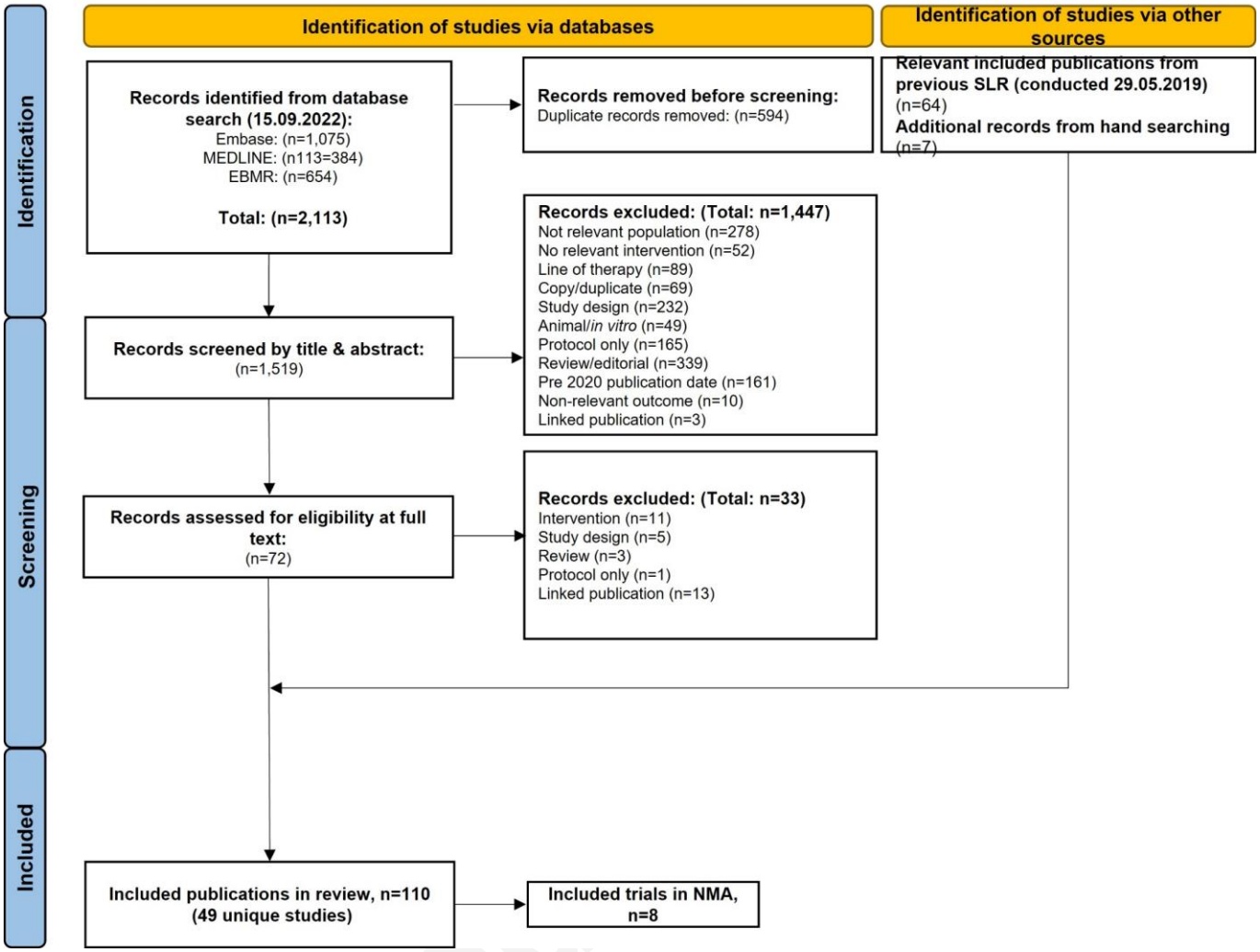
Identification
Screening
Included
Identification of studies via databases
Identification of studies via other sources
Records identified from database search (15.09.2022):
Embase: (n=1,075)
MEDLINE: (n113=384)
EBMR: (n=654)
Total: (n=2,113)
Records removed before screening:
Duplicate records removed: (n=594)
Relevant included publications from previous SLR (conducted 29.05.2019) (n=64)
Additional records from hand searching (n=7)
Records screened by title & abstract: (n=1,519)
Records excluded: (Total: n=1,447)
Not relevant population (n=278)
No relevant intervention (n=52)
Line of therapy (n=89)
Copy/duplicate (n=69)
Study design (n=232)
Animal/in vitro (n=49)
Protocol only (n=165)
Review/editorial (n=339)
Pre 2020 publication date (n=161)
Non-relevant outcome (n=10)
Linked publication (n=3)
Records assessed for eligibility at full text: (n=72)
Records excluded: (Total: n=33)
Intervention (n=11)
Study design (n=5)
Review (n=3)
Protocol only (n=1)
Linked publication (n=13)
Included publications in review, n=110 (49 unique studies)
Included trials in NMA, n=8

Table 1: NMA results: PFS & OS (atezolizumab plus bevacizumab versus comparators)

HR (95% CrI)–probability of A + B being superior	OS	PFS
A+ B versus sorafenib	0.68 (0.42–1.10); 96%	0.66 (0.27–1.59); 91%
A+ B versus cabozantinib	NA	0.93 (0.24, 3.44); 58%
A+ B versus cabozantinib + atezolizumab	0.75 (0.38–1.48); 83%	1.05 (0.29–3.88); 45%
A+ B versus camrelizumab + rivoceranib	1.09 (0.56–2.14); 37%	1.26 (0.34–4.60); 26%
A+ B versus durvalumab	0.79 (0.41–1.49); 81%	0.65 (0.17–2.29); 87%
A+ B versus durvalumab + tremelimumab	0.87 (0.45–1.66); 70%	0.73 (0.20–2.57); 81%
A+ B versus lenvatinib	0.74 (0.39–1.40); 87%	1.01 (0.27–3.63); 48%
A+ B versus lenvatinib + pembrolizumab	0.88 (0.40–1.49); 67%	1.22 (0.24–5.74); 32%
A+ B versus nivolumab	0.80 (0.42–1.49); 81%	0.71 (0.19–2.55); 83%
A+ B versus tislelizumab	0.80 (0.42–1.52); 80%	0.59 (0.16–2.10); 89%

Abbreviations: A + B, atezolizumab plus bevacizumab; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

Table 2: Summary of safety data reported by eligible studies in the network

Study	Treatment arm	Population	N analysed	All-grade TRAEs, n (%)	Grade 3-4 TRAEs, n (%)	All-grade TRSAEs, n (%)	Death due to AEs, n (%)	Treatment discontinuation due to AEs, n (%)
Yau (2022) [28] CheckMate 459	Nivolumab	ITT	367	257 (70)	81 (22.1)	43 (11.7)	4 (1.1)	27 (7.4)
	Sorafenib	ITT	363	338 (93.1)	179 (49.3)	39 (10.7)	1 (0.28)	42 (11.6)
Kelley (2022) [29] COSMIC-312	Cabozantinib plus atezolizumab	ITT	429	399 (93)	273 (63.6	78 (18)	51 (12)	Led to discontinuation, any treatment: 58 (14) Led to discontinuation, both treatments: 26 (6)
	Sorafenib	ITT	207	186 (90)	95 (45.9)	16 (8)	23 (11)	16 (8)
	Cabozantinib	ITT	188	178 (95)	113 (60.1)	24 (13)	30 (16)	16 (9)
Abou-Alfa (2022) [17] HIMALAYA	STRIDE	ITT	388	294 (75.8)	100 (25.8)	68 (17.5)	9 (2.3)	32 (8.2)
	Durvalumab	ITT	388	202 (52.1)	50 (12.9)	32 (8.2)	0 (0)	16 (4.1)
	Sorafenib	ITT	374	317 (84.8)	138 (36.9)	35 (9.4)	3 (0.8)	41 (11)
	T75 + durvalumab	ITT	152	106 (69.7)	32 (21.2)	28 (18.4)	2 (1.3)	13 (8.6)
Finn (2020) [8, 30] IMbrave150	Atezolizumab plus bevacizumab	Rest of ITT population (non-Vp4)	285	247 (87)	125 (44)	65 (23)	5 (2)	Led to discontinuation, any treatment: 61 (21)
	Sorafenib	Rest of ITT population (non-Vp4)	133	126 (95)	61 (46)	20 (15)	1 (1)	Led to discontinuation, any treatment: 16 (12)
Finn (2022) [31] LEAP-002	Lenvatinib plus pembrolizumab	ITT	395	381 (96.5)	243 (61.5)	NR	4 (1.0)	Led to discontinuation, any treatment: 71 (18) Led to discontinuation, both treatments: 22 (5.6)
	Lenvatinib plus placebo	ITT	395	378 (95.7)	224 (56.7)	NR	3 (0.8)	Led to discontinuation, any treatment: 42 (10.6) Led to discontinuation, both treatments: 18 (4.6)
Qin (2022) [32] NCT03764293	Camrelizumab plus rivoceranib	ITT	272	265 (97.4)	219 (80.5)	66 (24.3)	1 (0.4)	Discontinuation of any treatment components: 66 (24.3) Discontinuation of all treatment components: 10 (3.7)
	Sorafenib	ITT	269	249 (92.6)	140 (52)	16 (5.9)	1 (0.4)	Discontinuation of any treatment components: 12 (4.5) Discontinuation of all treatment components: 12 (4.5)
Qin (2022) [19] RATIONALE-301	Tislelizumab	ITT	338	259 (76.6)	NR	40 (11.8)	3 (0.9)	37 (10.9)
	Sorafenib	ITT	324	311 (96)	NR	33 (10.2)	2 (0.6)	60 (18.5)
Kudo (2018) [7] REFLECT	Lenvatinib	ITT	476	447 (94)	NR	84 (18)	11 (2)	63 (13.2)
	Sorafenib	ITT	475	452 (95)	NR	48 (10)	4 (1)	43 (9.1)

Abbreviations: AE, adverse event; ITT, intent to treat; NR, not reported; STRIDE, 300 mg of tremelimumab for one dose plus 1500 mg of durvalumab every 4 weeks; T75, 75 mg of tremelimumab every 4 weeks for four doses; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.