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Original Research

Comparative efficacy of novel combination strategies for unresectable hepatocellular carcinoma: A network metanalysis of phase III trials

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Abstract ***Background:*** Dual programmed cell death-1 and vascular endothelial growth factor pathway inhibition is the novel standard of care for patients with unresectable hepatocellular carcinoma. Direct comparisons between first-line treatments are lacking.
Method: We conducted a literature search in MEDLINE (https://pubmed.ncbi.nlm.nih.gov), the Cochrane library (https://www.cochranelibrary.com) and Embase (www.embase.com) between January 2007 and February 2022. We included phase III randomised controlled trials that tested immune-checkpoint inhibitors or tyrosine kinase inhibitors, including sorafenib, lenvatinib and donafenib, and evaluated as primary end-point overall survival (OS) or progression-free survival (PFS). Studies testing loco-regional therapies were excluded. The primary end-point was to compare the efficacy of first-line options in terms of OS and PFS. We extracted Hazard ratios (HR) and 95% confidence intervals (95% CI) for OS and PFS and performed a frequentist network meta-analysis with fixed effect multivariable meta-regression models. The research protocol was registered in PROSPERO, an international prospective register of systematic reviews (registration code CRD42022312489).

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Findings: Literature review yielded 13709 results, after duplicates removal and exclusion of not relevant studies, 70 papers were available for screening. After full-text review, 9 studies were eligible for analysis. Atezolizumab plus bevacizumab reduced the risk of death compared to placebo (HR 0·40; 95% CI 0·28-0·57), sorafenib (HR 0·58; 95% CI 0·42-0·80), lenvatinib (HR 0·63; 95% CI 0·44-0·89), atezolizumab plus cabozantinib (HR 0·64; 95% CI 0·43-0·97), nivolumab (HR 0·68; 95% CI 0·48-0·98) and donafenib (HR 0·69; 95% CI 0·48-0·99). Atezolizumab plus bevacizumab was not statistically superior to durvalumab plus tremelimumab (HR 0·74; 95% CI 0·52-1·06) and sintilimab plus IBI305 (HR 1·02; 95% CI 0·67-1·55) in reducing the risk of death. Efficacy was associated with a higher risk of grade 3 adverse events.

1. Introduction

After a decade of stagnation, dominated by the exclusive availability of sorafenib as a molecularly targeted therapy capable of conferring a significant survival benefit, the therapeutic landscape of unresectable hepatocellular carcinoma (uHCC) has rapidly evolved. In 2020, the Imbrave-150 trial has established for the first time the superiority of atezolizumab plus bevacizumab over sorafenib in the treatment of uHCC, leading to its global approval [1]. Evidence of efficacy from combined programmed cell death-1 and vascular endothelial growth factor (VEGF) inhibition has been independently validated in the ORIENT-32 trial, which tested the combination of sintilimab and IBI305 versus sorafenib in Asia [2].

The therapeutic landscape has recently become more complicated by the demonstration of a significant overall survival (OS) benefit from the combination of durvalumab plus tremelimumab, an anti-PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) combination tested against sorafenib in the HIMALAYA trial [3]. On the other hand, whilst capable of leading to a significant prolongation of PFS compared to sorafenib, the combination of cabozantinib plus atezolizumab did not improve OS at the first pre-planned analysis [4]. Taken individually, results of these trials are instigating profound changes in the therapeutic decision making for HCC, having led to the revision of treatment guidelines and staging algorithms including the Barcelona Clinic Liver Cancer (BCLC) system. However, a parallel reporting of several phase III development programs leaves practicing clinicians with unresolved questions as to the comparative efficacy of more modern immunotherapeutic combinations, for which head-to-head comparisons do not exist and are unlikely going to be planned in the future [5].

Network meta-analyses (NMA) represent an optimal methodology to systematically review and summarise the evidence available in support of the use diverse therapeutic strategies where direct comparison was not pursued in prospective studies [6]. In the present study, we performed a NMA to compare the survival outcomes (OS and PFS), objective response rates (ORRs) and safety profiles (adverse events-AEs) of randomised control trial investigating first-line systemic therapy options for HCC from 2007 to 2022.

2. Methods

2.1. Search strategy and selection criteria

We conducted a network metanalysis to compare first-line systemic therapies for uHCC. Studies were included in the network meta-analysis if: (i) were phase III randomised controlled trials, (ii) considered as interventions immune-checkpoint inhibitors (ICIs) or tyrosine kinase inhibitors including sorafenib, lenvatinib and donafenib evaluated as first-line monotherapy, (iii) evaluated as primary end-point OS or PFS. Studies testing loco-regional therapies alone or in combination with systemic treatment were excluded. Literature search was carried out in MEDLINE (https://pubmed.ncbi.nlm.nih.gov), the Cochrane library (https://www.cochranelibrary.com) and Embase (www.embase.com) between the 1st of January 2007 and the 28th of February 2022; research was restricted to studies published in English only. Conference proceedings published until the 28th February 2022 were also retrieved from the following major scientific societies in the field of oncology including the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD). The complete the search strategy is reported in the Supplementary. Literature search was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria [7]. Two authors (CAMF and AD) evaluated independently the studies eligibility for the inclusion in the network meta-analysis on the basis of the PICO

(patients, interventions, comparison and outcome) framework and inclusion and exclusion criteria. Controversies in the adjudication of studies were discussed and resolved with the contribution of a third independent author (DJP). The research protocol was registered in PROSPERO, an international prospective register of systematic reviews (registration code CRD42022312489; https://www.crd.york.ac.uk/prospero/#searchadvanced).

2.2. Data analysis

The risk of bias was evaluated according to the Cochrane risk of bias assessment tool [8]. The tool identifies 7 domains investigating different aspects related to the design, conduction and reporting of randomised controlled trials. To each item is assigned a judgement as 'Low' or 'High'. Details about the risk of bias assessment are available in Supplementary. From the retrieved studies, primary data were extracted and populated in customised data collection spreadsheet. Details about searching strategy and data collection are available in Supplementary. A frequentist network meta-analysis was performed to compare (a) the efficacy of different treatments for uHCC in term of OS, PFS and ORR; (b) the safety of each treatment according to the incidence of all grade AEs, grade 3 or higher AEs and AEs leading to treatment discontinuation. To perform the analyses, the data on ORR and AEs by treatment reported in the included studies were used to calculate the odds ratios (ORs) and relative risks (RRs) and the corresponding 95% confidence intervals (CIs) for the association between the treatment and probability of complete or partial response and treatment and risk of AEs, respectively. Fixed effect multivariable meta-regression models were performed to estimate the indirect hazard HRs and ORs or RR and corresponding 95% CI. Two analyses were performed; the first one was aimed to compare the efficacy of atezolizumab plus bevacizumab versus all other treatments while the second one was aimed to compare all treatments with placebo. Adverse events of all arms were compared with placebo. Forest plots were drawn to synthetise the results obtained for the comparisons of interest. Treatments were ranked according to their probability of being the best treatment based on the P-scores which measure the extent of certainty that a treatment is better than another one, averaged over all competing therapies. Since recent evidence suggest a role of HCC aetiology in determining outcomes to immunotherapy, and non-viral patients have been described to have worse survival compared to patients with viral hepatitis [9], we conducted subgroup analyses for OS in viral and non-viral patients. Details about the subgroup analysis are reported in Supplementary. The analysis was performed using the meta and netmeta packages in R, version 4.1.2.

3. Results

As reported in Fig. 1, literature review yielded 13,709 results, after duplicates removal and exclusion of non-relevant studies (Fig. 1A), 70 papers were available for screening. Following review in full-text form, 58 studies were removed and other 7 were included after performing hand search of relevant abstracts. Among the 19 studies left, a further 10 studies were removed due to not relevant outcomes, design or intervention, leaving the following 9 phase III clinical trials for the NMA: SHARP [10], Asia Pacific [11], REFLECT [12], CheckMate 459 [13], IMbrave150 [1], ORIENT-32 [2], HIMALAYA [3], COSMIC-312 [4] and the Qin *et al.*, 2021 study [14], which tested respectively: sorafenib vs placebo (SHARP and Asia Pacific), lenvatinib vs sorafenib, nivolumab versus sorafenib, atezolizumab plus bevacizumab versus sorafenib, sintilimab plus IBI305 versus sorafenib, durvalumab plus tremelimumab versus sorafenib, atezolizumab plus cabozantinib versus sorafenib and donafenib versus sorafenib, as first-line systemic treatments for uHCC. COSMIC-312 [4] and HIMALAYA [3] included three arms of treatment; however, since one arm (sorafenib) was available for comparison, only atezolizumab plus cabozantinib and durvalumab plus tremelimumab were, respectively, considered in the NMA.

Overall, 6272 patients were included in the analysis; among them, 5896 patients received active treatment and 376 patients received placebo. Sorafenib was the control arm of all the trials, except for the SHARP and Asia Pacific studies, which investigated sorafenib against placebo. Donafenib and lenvatinib were tested for non-inferiority against sorafenib, whereas all the other studies were powered to demonstrate superiority of the experimental arm over controls. At the time of reporting, median follow-up for the experimental arm was shorter for the IMbrave-150 (8·9 months) than HIMALAYA (33·2 months), REFLECT (27·7 months), ORIENT-32 (15·8 months), COSMIC-312 (15·8 months) and CheckMate 459 (15·2 months). We report inter-trial differences in the inclusion criteria and in stratification strategies (Supplementary Table 1), responsible, at least in part for imbalances in baseline characteristics of the patient populations.

As shown in Supplementary Table 2, salient differences included an inferior median age for the ASIA Pacific, ORIENT-32 and Qin *et al.* studies compared to the other trials; a higher proportion of patients from Western countries except for the ASIA Pacific [11], ORIENT-32 [2] and Qin *et al.* [14], which were exclusively conducted in Asia, and for the REFLECT study [12]. The prevalence of portal vein invasion at baseline was inferior in patients enrolled in REFLECT [12], HIMALAYA [3] and ORIENT-32 [2]: this was due to trial inclusion criteria, in fact the REFLECT and

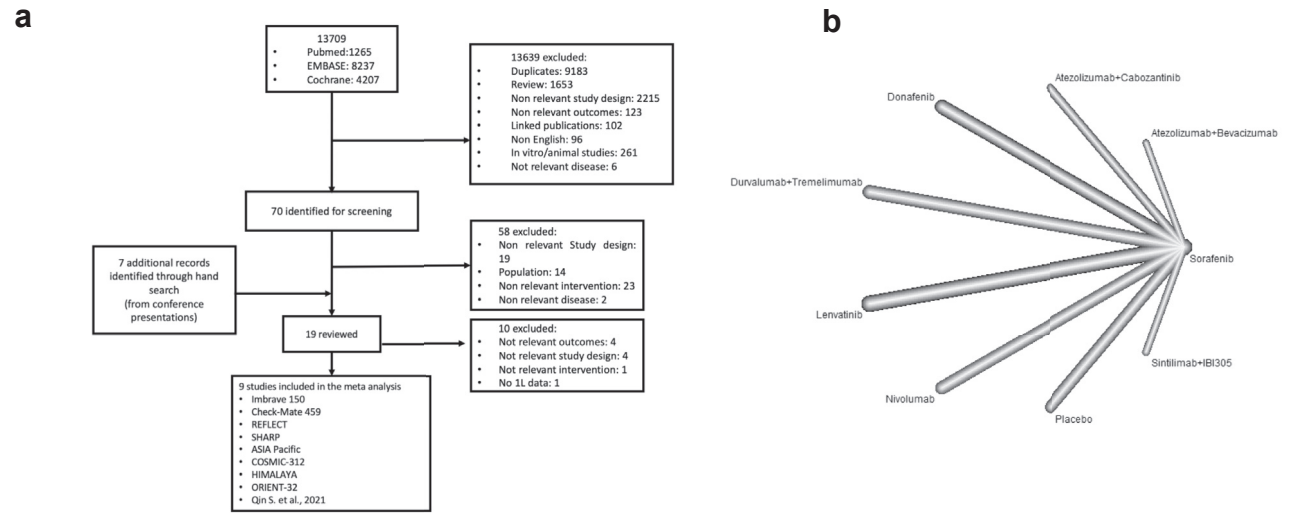


Fig. 1. **PRISMA graph and network plot summarising the studies included in the network metanalysis**, (**a**) PRISMA graph reporting the selection of the studies; (**b**) network plot including the treatments included in the analysis.

HIMALAYA studies did not include patient with portal vein invasion at Vp4. Overall, almost all the patients had preserved liver function according to Child-Pugh score (A), a small percentage of participants (<5%) enrolled in the following studies had Child-Pugh B7: SHARP [10], ASIA Pacific [11], REFLECT [12], CheckMate 459 [13], ORIENT-32 [2] and Qin *et al.* [14].

Aetiology of chronic liver disease was heterogeneous across subgroups, with viral being higher in studies exclusively conducted in Asia. All the studies were evaluable for OS and PFS. Responses were measured according to RECIST criteria in SHARP and Asia Pacific, all the other trials adopted RECIST 1.1; mRECIST assessment was also performed in the IMbrave150 [1]; ORIENT-32 [2] and REFLECT [12]; we selected ORR according to RECIST and RECIST 1.1 as reference method to allow for reproducible comparison across trials.

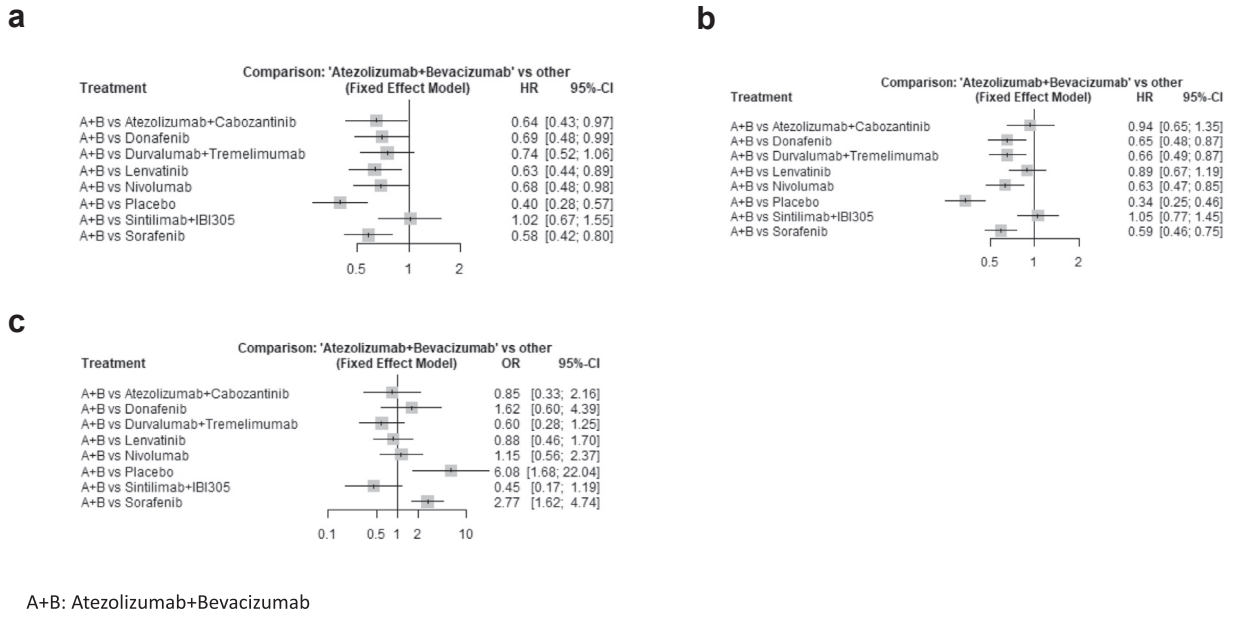
Regarding the risk of bias assessment, we found that the risk of bias was generally low across all the studies, with all the trials reporting low risk in at least 5 out of 7 domains. The absence of blinding at allocation represented the major risk of bias for all the studies, apart from the SHARP [10] and Asia Pacific [11], wherein patients and investigators were masked to the treatment given. Blinded Independent radiologic review was performed in all the trials except for the HIMALAYA [3]. Details about the risk of bias for each study are reported in Supplementary Table 3.

Fig. 1B shows the network plot of the included studies: 9 studies were included in the NMA, all included as treatment arm Sorafenib.

When evaluating HRs for OS, considering atezolizumab plus bevacizumab as exposure arm and all other treatments as comparators, we found that it reduced the risk of death by 60%, 42%, 37%, 36%, 32%, and 31%, when compared to placebo (HR 0·40; 95%CI 0·28-0·57), sorafenib (HR 0·58; 95%CI 0·42-0·80), lenvatinib (HR 0·63; 95%CI 0·44-0·89), atezolizumab plus cabozantinib (HR 0·64; 95%CI 0·43-0·97), nivolumab (HR 0·68; 95%CI 0·48-0·98) and donafenib (HR 0·69; 95%CI 0·48-0·99), respectively. Atezolizumab plus bevacizumab was not significantly superior to the combination of durvalumab plus tremelimumab (HR 0·74; 95%CI 0·52-1·06), whereas the efficacy of atezolizumab plus bevacizumab was comparable to that of sintilimab plus IBI305 (HR 1·02; 95%CI 0·67-1·55, Fig. 2A).

In our analysis, all the treatments showed a significant survival advantage compared to patients treated with placebo, with the greatest risk reduction provided by atezolizumab plus bevacizumab (HR 0·40; 95%CI 0·28-0·57) and sintilimab plus IBI305 (HR 0·39; 95%CI 0·28-0·55), followed by durvalumab plus tremelimumab (HR 0·54; 95%CI 0·42-0·69) (Supplementary Fig. 1A). The p-scores which ranked all therapeutic options for their probability of being the most effective option in reducing the risk of death (Table 1), PD-1/VEGF combinations including sintilimab plus IBI305 (94% probability) and atezolizumab plus bevacizumab (93% probability) achieved the highest probability scores. All the immunotherapy-based options, either in combination or as monotherapy, scored higher than Tyrosine kinase inhibitors (TKIs) according to the p-score ranking.

We subsequently analysed PFS, considering atezolizumab plus bevacizumab as exposure and all other treatments as reference. We found that treatment with atezolizumab plus bevacizumab significantly reduced the risk of progression compared to placebo (HR 0·34; 95%CI 0·25-0·46), donafenib (HR: 0·65; 95% CI 0·48-0·87), sorafenib (HR 0·59; 95%CI 0·46-0·75) and nivolumab (HR 0·63; 95%CI 0·47-0·85) (Fig. 2B). Comparing all the treatments against placebo,



A+B: Atezolizumab+Bevacizumab

Fig. 2. **Forest plot for overall survival, progression-free survival and objective response rate**, (**a**) Forest plot for overall survival (OS) considering atezolizumab plus bevacizumab as exposure and all other treatments as reference; (**b**) forest plot for progression-free survival (PFS) considering atezolizumab plus bevacizumab as exposure and all other treatments as reference; (**c**) Forest plot for objective response rate (ORR) considering atezolizumab plus bevacizumab as exposure and all other treatments as reference.

atezolizumab plus bevacizumab and sintilimab plus reduced the risk of progression by 66% (HR: 0·34 95% CI 0·25-0·46) and 68% (HR: 0·32 95%CI 0·24-0·43), respectively. Lenvatinib and atezolizumab plus cabozantinib provided a reduction in the risk of progression by 62% (HR: 0·38; 95%CI: 0·30-0·49) and 64% (HR: 0·36; 95%CI 0·26-0·51) (Supplementary Fig. 1B), respectively. According to p-scores for PFS (Table 1), the combination of sintilimab plus IBI305 was associated with the highest chance of being the most effective treatment in reducing the risk of progression (89%), followed by atezolizumab plus bevacizumab (84%) and atezolizumab plus cabozantinib (77%), whose probability was very similar to that of lenvatinib.

Indirect comparison of ORR, according to RECIST 1.1 or RECIST criteria (SHARP and ASIA Pacific), showed that atezolizumab plus bevacizumab had higher chances of leading to a measurable radiological response compared to sorafenib (OR:2·77; 95%CI 1·62- 4·74) and placebo (OR: 6·08; 95%CI 1·68-22·4) (Fig. 2C) and all the treatments were more effective than placebo in achieving objective response (Supplementary Fig. 1C). Sintilimab plus IBI-350 reported 93% probability in being the most effective option in achieving radiological responses (Table 1). Detailed ORRs for each treatment arm is summarised in Table 2.

A subgroup analysis was performed to assess differences in OS according to HCC aetiology. We found that the distribution of different aetiologist among trials was heterogeneous (Supplementary Table 2), and only COSMIC-312 [4] and HIMALAYA [3] were stratified according to disease aetiology (HBV; HCV and non-

Table 1
Ranking of the available treatment according to their probability of being the best.

Overall survival		Progression-free survival		Objective response rate	
Treatment	p-score	Treatment	p-score	Treatment	p-score
Sintilimab + IBI305	0·9413	Sintilimab + IBI305	0·8901	Sintilimab + IBI305	0·9271
Atezolizumab + Bevacizumab	0·9276	Atezolizumab + Bevacizumab	0·8382	Durvalumab + tremelimumab	0·8096
Durvalumab + Tremelimumab	0·6933	Lenvatinib	0·7726	Durvalumab	0·7104
Nivolumab	0·5413	Atezolizumab + Cabozantinib	0·7722	Atezolizumab + cabozantinib	0·6142
Durvalumab	0·5182	Durvalumab	0·4811	Lenvatinib	0·5931
Atezolizumab + Cabozantinib	0·4258	Durvalumab + Tremelimumab	0·4072	Atezolizumab + bevacizumab	0·5143
Donafenib	0·4006	Nivolumab	0·3733	Nivolumab	0·4280
Lenvatinib	0·3761	Sorafenib	0·2422	Donafenib	0·2809
Sorafenib	0·1755	Donafenib	0·2226	Sorafenib	0·1157
Placebo	0·0002	Placebo	0·0006	Placebo	0·0066

Probability (p-score) for each treatment to be the best in terms of overall survival; progression-free survival and objective response rate.

Table 2
Descriptive incidence of adverse events according to NCTCA and ORR according to RECIST criteria.

Study	Arm	Any grade AE N (%)	Grade ≥3 AEs N (%)	AEs requiring treatment discontinuation (%)	ORR RECIST % (95% CI)
REFLECT	Lenvatinib	470 (99%)	357 (75%)	42 (9%)	18.8% (15.3–22.3)
	Sorafenib	472 (99%)	316 (67%)	34 (7%)	6.5% (4.3–5.14)
ImBrave-150	Atezolizumab + Bevacizumab	323 (98.2%)	186 (61.1%)	51 (15.5%)	27.3% (22.5–32.5)
	Sorafenib	154 (98.7%)	86 (60.9%)	16 (10.3%)	11.9% (7.4–18)
COSMIC	Atezolizumab + Cabozabtinib	93%	63.5%	6.1%	11.2% (8.1–14)
	Sorafenib	90%	41%	7.7%	3.7% (1.6–7.1)
HIMALAYA	Durvalumab + Tremelimumab	378 (97.4%)	196 (50.5%)	32 (8.2%)	20.1%
	Sorafenib	357 (95.5%)	196 (52.4%)	41 (11%)	5.1%
	Durvalumab	345 (88.9%)	144 (37.1%)	16 (4.1%)	17%
Check-Mate 459	Nivolumab	257 (70%)	82 (22.3%)	27 (7.4%)	15% (12–19)
	Sorafenib	338 (93.1%)	180 (49.5%)	42 (11.6%)	7% (5–10)
SHARP	Sorafenib	98%	45%	34 (11%)	2%
	Placebo	96%	32%	15 (5%)	1%
ASIA Pacific	Sorafenib	146 (98%)	71 (serious) (47.7%)	29 (19.5%)	3.3%
	Placebo	71 (94.7%)	34 (serious) (45.3%)	10 (13.3%)	1.3%
ORIENT-32	Sintilimab plus IBI305	376 (99%)	207 (54%)	52 (14%)	21% (17–25)
	Sorafenib	181 (98%)	87 (47%)	11 (6%)	4% (2–8)
Qin S. *et al.*, 2021	Donafenib	332 (100%)	191 (57%)	34 (10%)	4.6%
	Sorafenib	329 (99%)	224 (67%)	42 (13%)	2.7%

Number and percentage (%) of patients experiencing adverse events (AEs) of any grade, of grade 3 or higher and AEs requiring permanent treatment discontinuation in each treatment arm; objective response rate (ORR) and its 95%CI according to RECIST criteria for each treatment arm.

viral). We, therefore, compared OS in viral and non-viral patients in the following trials: IMbrave150 [1], REFLECT [15], COSMIC-312 [4], HIMALAYA [3] and CheckMate 459 [13]; the remaining studies (SHARP, ASIA Pacific, ORIENT-32 and Qin *et al.*) were not included due to the absence of data for each subgroup of interest. As reported in previous section, indirect estimates of HRs for viral patients were calculated from HRs for HBV and HCV. In keeping with previously published evidence, we found that atezolizumab plus bevacizumab did not significantly reduce the risk of death compared to other arms in non-viral patients (Supplementary Fig. 2A). When considering only viral (HBV + HCV) patients, atezolizumab plus bevacizumab was confirmed to significantly reduce the risk of death compared to sorafenib, lenvatinib and durvalumab plus tremelimumab (Supplementary Fig. 2B).

Safety was evaluated according to the incidence of AEs of all cause, which were classified according to NCI Common Terminology Criteria for Adverse Events versions 3 (ASIA Pacific and SHARP), 4 (IMbrave150, REFLECT, CheckMate 459, Qin *et al.*) and 5 (ORIENT-32, COSMIC and HIMALAYA). For the ASIA Pacific study [11], the incidence of grade 3 or higher AEs was not available. We therefore considered the incidence of serious AEs, defined per study protocol as those that were life-threatening, resulted in death, required patient hospitalisation or prolongation of hospitalisation, or resulted in a persistent or significant disability or incapacity. The descriptive incidence of AEs for each treatment arm is reported in Table 2.

When considering toxicities of all grades (Supplementary Fig. 3), nivolumab (RR: 0·75; 95%CI: 0·70-0·81) was found to be associated with a reduced risk of all grade toxicities compared to placebo. We then compared the incidence of grade 3 or higher AEs and of AEs leading to permanent treatment discontinuation of all treatments, considering placebo as our reference subgroup (Fig. 3A and B).

Nivolumab was found to be associated with the lowest risk of grade 3 or higher adverse events (RR: 0·44; 95% CI: 0·34-0·56) (Fig. 3A), whereas atezolizumab plus cabozantinib (RR: 1·62; 95% CI: 1·26-2·09) reported the higher probability of grade 3 or higher AEs (Fig. 3A). Sintilimab plus IBI-305 (RR: 4·34; 95% CI: 2·02–9·33) and atezolizumab plus bevacizumab (RR: 2·85; 95% CI: 1·43-5·67) were associated with the highest probability of AEs leading to treatment discontinuation compared to placebo, followed by lenvatinib (RR: 2·33; 95%CI: 1·25-4·31) and sorafenib

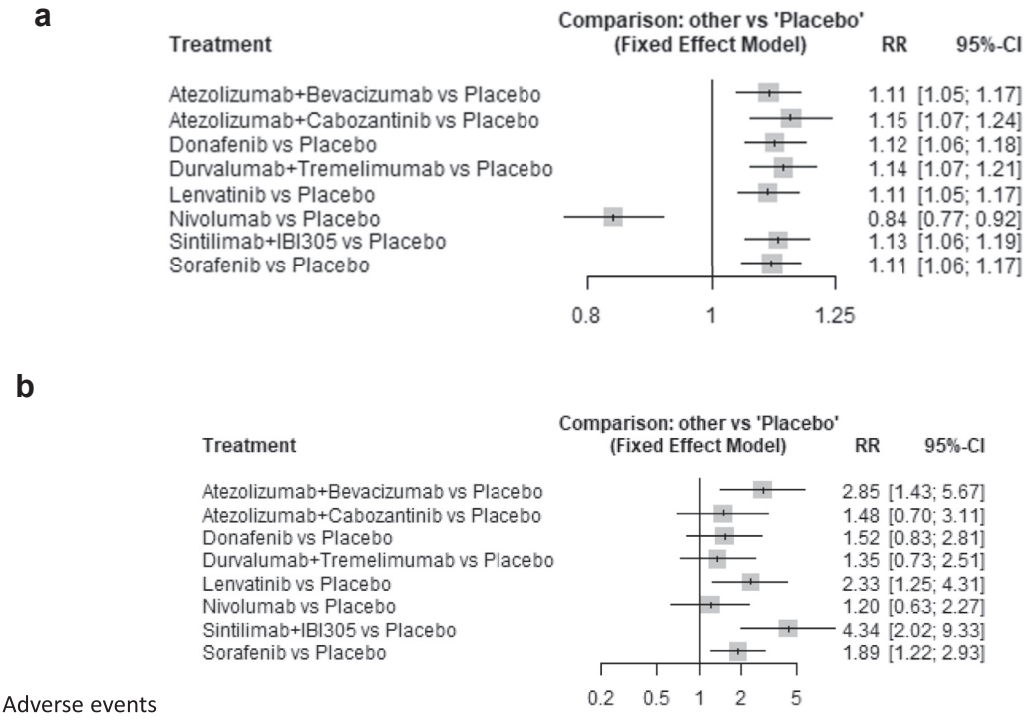


Fig. 3. **Forest plot for grade adverse events**, (**a**) forest plot for adverse events (AEs) of grade 3 or higher, considering all other treatments as exposure and placebo as reference; (**b**)forest plot for adverse events (AEs) leading to permanent treatment discontinuation, considering all other treatments as exposure and placebo as reference.

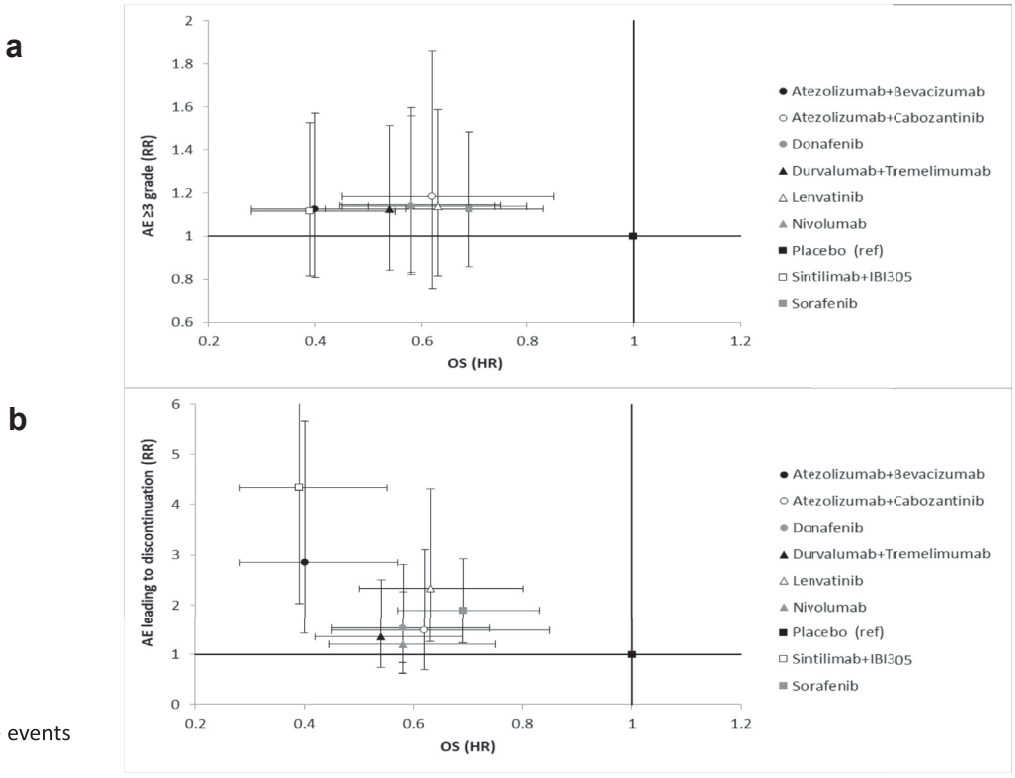


Fig. 4. **Joint evaluation of efficacy and safety of the different therapeutic strategies for unresectable HCC**, (**a**) Graph reporting hazard Ratios (HRs) for overall survival (OS) and relative risk (RR) for adverse events (AEs) of grade 3 or higher, considering placebo as reference; (**b**) graph reporting hazard ratios (HRs) for overall survival (OS) and relative risk (RR) for adverse events (AEs) leading to treatment discontinuation, considering placebo as reference.

(RR: 1·89; 95% CI: 1·22-2·93); whereas no increased risk of AEs causing treatment discontinuation was observed for atezolizumab plus cabozantinib (RR: 1·48; 95% CI: 0·70-3·11) and durvalumab plus tremelimumab (RR: 1·35; 95% CI: 0·73-3·11) (Fig. 3B). Overall, ICI monotherapy appeared to have the best safety profile compared to ICI-based combinations and TKIs.

Fig. 4 reports a graphical joint investigation of treatments' efficacy and safety.

4. Discussion

For decades, systemic therapy has played a modest role in the management of HCC. The advent of TKI therapy in 2007 ushered the way to a gradual widening of therapeutic options across multiple lines of therapy. As a result, patients whose disease carried a dismal prognosis of less than 7 months in the absence of effective treatment [15] can now hope for median OS figures that approach 2 years [16,17]. Treatment decisions in first-line carry an important weight in defining the oncological plan of care for each individual patient. On one hand, the high attrition in patients' candidacy to second-line therapies emphasises the need for highly effective first-line options to maximise long-term survivorship [18]. Second, the diverse adverse event profile of immune-based therapies, VEGF inhibitors and TKIs highlights the necessity to carefully weigh the predicted benefit of each therapeutic approach against the need to preserve patients from potential treatment-induced harm [19].

In this NMA, which includes 9 high-quality trials of first-line systemic therapies for unresectable HCC, we demonstrate that the combination of a PD-1/PD-L1 pathway inhibitor with a VEGF antagonist is the most effective therapeutic strategy in reducing the risk of progression or death. Comparison of ORR across studies shows that sintilimab plus IBI-305 and durvalumab plus tremelimumab provide the highest probability of achieving radiological response and all the treatments apart from sorafenib perform significantly better than placebo in inducing a radiologically appreciable reduction in disease burden.

Despite differences in inclusion criteria between trials, our NMA demonstrated that VEGF blockade with atezolizumab plus bevacizumab or sintilimab plus IBI-305 was not statistically superior to dual inhibition of the PD-1 and CTLA-4 checkpoints in terms of OS.

Atezolizumab plus bevacizumab therapy has rapidly replaced universal first-line TKI use following the demonstration of improved OS, PFS, ORR [1] and quality of life [20] compared to sorafenib. Evidence of non-significant superiority of PD-1/VEGF over PD-1/CTLA-4 blockade is of particular interest in a setting where direct comparison in randomised clinical trials does not exist. Co-inhibition of VEGF or CTLA-4 in conjunction with PD-1 pathway blockade affects a biologically diverse spectrum of negative regulators of anti-cancer immunity including – amongst others – impaired vascular permeability, regulatory T-cell proliferation, dendritic cell maturation [21].

The relative importance and contribution of VEGF versus CTLA-4-related mechanisms of immune reconstitution in improving survival outcomes is largely unknown in HCC [22], a disease where therapeutic decisions are not supported by predictive biomarkers of response in routine clinical practice [23]. In a context that is largely dominated by empirical prescribing and in absence of head-to-head comparisons, results from our metanalysis may be helpful in positioning both PD-1/VEGF and PD-1/CTLA-4 blockade as highly effective and potentially non-inferior therapeutic strategies in previously untreated uHCC, facilitating clinicians in recommending either therapy on the basis of the individual patients' suitability.

A point of great contention is whether aetiology of chronic liver disease influences response to ICI therapy in HCC [24]. When stratifying patients according to viral versus non-viral aetiology, the clear superiority of atezolizumab plus bevacizumab over other therapies demonstrated in the overall population fell short of statistical significance in non-viral patients, in keeping with previous evidence suggesting reduced efficacy of immunotherapy in this patient subset [9]. Unlike previous metanalyses that first highlighted differences in efficacy in viral versus non-viral patients, the present NMA exclusively focused on first-line therapies and expanded the observation to therapeutic combinations not covered in previous work.

Whilst provocative, our data on viral subgroups rest on primary evidence from only 6 out of 9 studies for which reliable labelling of non-viral aetiology was recorded. In addition, none of the studies except for COSMIC-312 [4] and HIMALAYA [3] were stratified according to aetiology, leading to inter-trial heterogeneity. As such, our findings remain hypothesis generating and although not aiming to change the interpretation of primary trial data, they suggest the need to incorporate viral aetiology as pre-planned stratification factor in future clinical studies.

Alongside efficacy considerations, adverse events are an important choice factor in first-line systemic therapy of HCC.

In our comparative assessment of the clinical value of diverse therapeutic regimens, we assessed each therapy for the proportion of AEs graded 3 or higher and rates of permanent cessation due to AEs. In our study, anti-PD-1 therapy with nivolumab was associated with a lower proportion of AEs, whereas among ICI combinations, durvalumab plus tremelimumab reported the

lowest risk of AEs. Whilst failing to demonstrate a significant survival benefit in first-line [13], PD-1 inhibition is known for its wide therapeutic index, which makes this option suitable in elderly [25] and frailer patients including those with liver dysfunction [26–28]. Evidence of non-inferiority for durvalumab monotherapy against sorafenib [3] and prospective reporting of the phase III RATIONALE 301 study [29] will aid in further defining the role of ICI monotherapy in this setting.

When considering combination therapy, we found that dual checkpoint inhibition with durvalumab and tremelimumab demonstrated a lower proportion of AEs and permanent discontinuations due to toxicity than PD-1/VEGF combinations and the PD-1/TKI combination with cabozantinib, for which rates of toxicity was higher. Whilst each drug is characterised by intrinsically different mechanisms of toxicity, which makes it difficult to standardise cross-trial comparison [30], our findings contribute to highlight the challenge stemming from additive and non-overlapping toxicity stemming from exposure to combinations with anti-angiogenics and TKIs, whilst supporting the tolerability of the single priming dose of anti-CTLA-4 which prevents the high proportion of high-grade toxicity events seen in other tumour types [31].

Our NMA of landmark phase III trials of HCC recognises a number of limitations. When considering our efficacy analyses, it is important to highlight that OS remains the most objective method to perform indirect comparisons of efficacy [32], despite being potentially influenced by length of follow-up, cancer-unrelated mortality and exposure to subsequent lines of therapy. This is aspect is particularly important when comparing estimates from older TKI studies versus ICI combinations, given the lack of effective second-line options until 2017 [33]. Caution is also required when comparing PFS across studies in view of its reliance on the subjective evaluation of response, timing of radiological assessment and different mechanisms of action of each study drug.

Whilst general consensus suggests that HR for PFS$\leq$0·6 are highly likely to translate in OS benefit [34], recent evidence from HIMALAYA [3], where OS was met in the absence of PFS benefit and COSMIC-312 [4], where PFS benefit did not translate into OS improvement suggests the possibility of response-independent effects on survival which are still poorly understood. Lack of blinding in all but two studies raise the possibility of observer bias in our ORR analysis. However, all protocols except from HIMALAYA [3] required blinded radiological review, therefore considerably reducing this risk. Other limitations apply to ORR analysis and should prompt caution in the interpretation of indirect comparisons across studies. First, none of the studies was powered to demonstrate superiority in ORR. Secondly, although ICIs use has been associated with a higher proportion of ORR, the low proportion of ORR in previous studies has questioned its reliability as a true surrogate of OS [34]. In addition, international guidelines advise to adopt both RECIST and mRECIST criteria to assess response in HCC [35]. However, not all the studies utilised mRECIST assessment and NMA was based on RECIST and RECIST 1.1 criteria, which were originally validated to define response to cytotoxic chemotherapy [35] and might not be appropriate to adequately assess the response of intra-hepatic lesions [36].

In conclusion, this NMA provides strong and reproducible evidence to support the efficacy of ICI plus anti-VEGF combinations as first-line treatment for unresectable/advanced HCC. Within the limits of cross-trial comparisons, our estimates of survival suggest that the efficacy of PD-1/VEGF and PD-1/CTLA-4 blockade could be similar. Whilst anti-PD-1 therapy remains the most favourable from a safety standpoint, the improved efficacy from ICI combinations comes at the price of greater risk of high-grade toxicity, often leading to permanent cessation. The emergent finding of differential therapeutic efficacy in patients with viral versus non-viral HCC calls for integration of viral status as a stratifying factor in subsequent studies. Further research on mechanisms of response and resistance to ICI combinations are required to facilitate rationale positioning of immunotherapy across whole spectrum of chronic liver disease.

Contributors

CAMF did study concept and design, acquisition of data, data analysis and interpretation, statistical analysis and manuscript draft; AD did study concept and design and acquisition of data; AC did the statistical analysis; LS did the statistical analysis and supervised the study; COD did analysis and interpretation of data and manuscript draft; AG did analysis and interpretation of data; AC did acquisition of data and supervised the study; DJP did study concept and design, acquisition of data, manuscript draft and supervised the study.

All the authors have full access to all data in the study.

Interpretation

PD-1 plus VEGF pathway blockade leads to the highest reduction in the risk of death compared to other regimens in uHCC, at the price of higher toxicity.

Role of the funding source

There was no funding source for this study.

Data sharing

Statistical analysis data will be shared upon request to the authors after publication.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

DJP received lecture fees from ViiV Healthcare and Bayer Healthcare and travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, and Astra Zeneca; received research funding (to institution) from MSD and BMS. AC received grant consultancies from MSD, Astrazeneca, Roche and BMS. He also received speaker's fees from Novartis, Astrazeneca and EISAI. AG has declared consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, EISAI, and Daichii Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, Astra Zeneca, Celgene, and Daichii Sankyo; research funds: EISAI, Eli Lilly, and Roche.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.06.058.

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