Comparative efficacy of novel combination strategies for unresectable hepatocellular carcinoma (HCC): a network metanalysis of phase III trials

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in the trials of interest**.**

Supplementary methods 1. Search terms applied to publication databases

1. exp Carcinoma, Hepatocellular/ or exp Liver Neoplasms
2. HCC
3. (hepat* or liver) adj3 (neoplasm* or cancer* or tumo?r* or malignan* or carcinoma*)
4. 1 or 2 or 3
5. exp Sorafenib/
6. (sorafenib or nexavar*)
7. Exp Atezolizumab/
8. (atezolizumab or tecentriq* or mpdl 3280* or mpdl3280* or rg 7446 or rg7446)
9. exp Nivolumab/
10. (nivolumab or opdivo* or 'bms-936558' or 'mdx-1106' or 'ono-4538' or 'bms936558' or 'mdx1106' or 'ono4538')
11. exp Bevacizumab/
12. (bevacizumab or avastin*)
13. (lenvatinib or lenvima* or kisplyx* or 'e 7080' or 'e7080')
14. exp Durvalumab/
15. (durvalumab or imfinzi* or medi4736 or medi-4736)
16. exp Tremelimumab/
17. (tremelimumab or cp-675206*)
18. exp Sintilimab/
19. (sintilimab or tyvyt* or ibi308*)
20. exp IBI305/
21. exp Donafenib/
22. (donafenib or cm 4307 or donafenib tosilate or donafenib tosylate or zeprosen* or zeprosyn*)
23. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomi#ed.ab.
27. placebo.ab.
28. randomly.ab.
29. clinical trials as topic.sh.
30. trial.ti.
31. 24 or 25 or 26 or 27 or 28 or 29 or 30
32. 4 and 23 and 31

Research performed in MEDLINE; EMBASE and Cochrane Library. Search is restricted to articles in English, published between January 2007 and February 2022.

Supplementary methods 2. Searches examined in hand search.

1. Scientific conference presentations (2007–2022):
    - European Society for Medical Oncology
    - American Society of Clinical Oncology (including the Gastrointestinal Cancers Symposium)
    - European Association for the Study of the Liver
    - American Association for the Study of Liver Diseases

Supplementary methods 3. Data collection strategy.

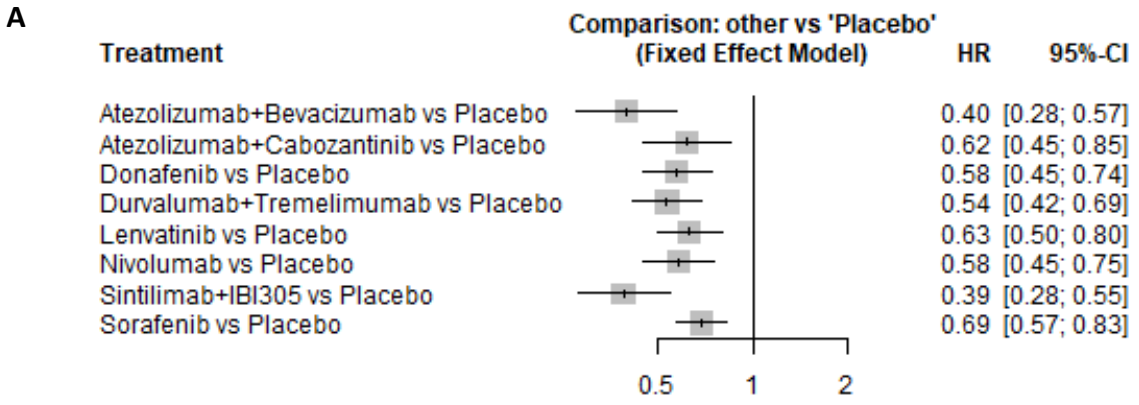
The following data were considered: study name and/or lead author name, publication year, characteristics of experimental and control arms, age of participants at study enrolment, proportion of subjects: i) living in western regions, ii) with microvascular invasion (MVI), iii) with extra-hepatic spread (EHS), iv) with viral aetiology, v) with Child Pugh A liver dysfunction, vi) with ECOG status equal to 0 and vii) HCC staging according to BCLC system. Data on best overall radiologic response to treatment and overall response rates (ORR) were collected in parallel. Moreover, the number and percentage of subjects who experienced AEs of any grade, AEs of grade 3 or higher and AEs leading to treatment discontinuation was retrieved for each treatment arm. In our comparative analysis of safety outcomes, we intended to account for adverse events potentially related to the underlying liver disease and underlying progressive malignancy, which contributes to influence prognosis and quality of life in HCC patients. We therefore considered AEs of all type rather than focusing only on treatment-related AEs. Lastly, we collected hazard ratios (HRs) and corresponding 95% confidence intervals (95%CI) for the association between treatments and OS and PFS.

Supplementary methods 4. Subgroup analysis**.**

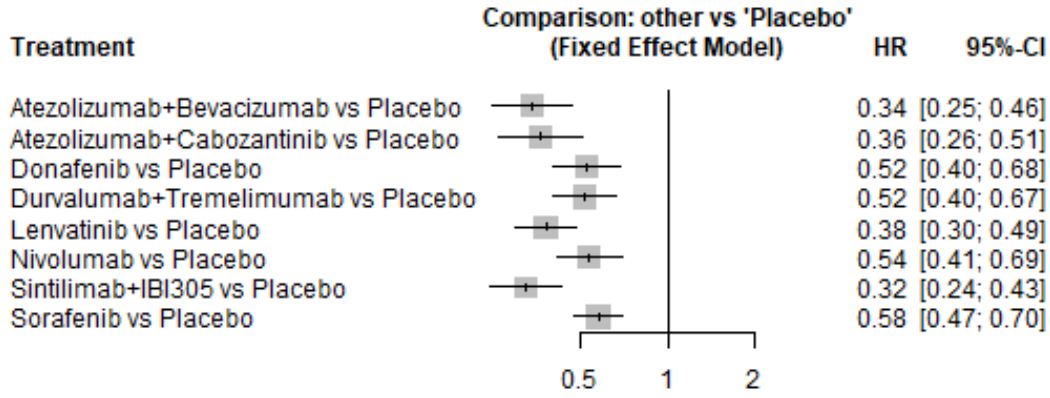
For the subgroup analysis, HRs for non-viral patients were directly extracted from each study, whereas, as reported in similar studies [1], HRs for the viral subgroup were calculated from HRs for HBV and HCV subgroups, using fixed effect meta-analysis based on estimates HRs and their standard errors. Data of non-viral patients treated with placebo were not available, therefore the efficacy analysis in this subgroup was only conducted against atezolizumab plus bevacizumab.

Supplementary Figure 1.

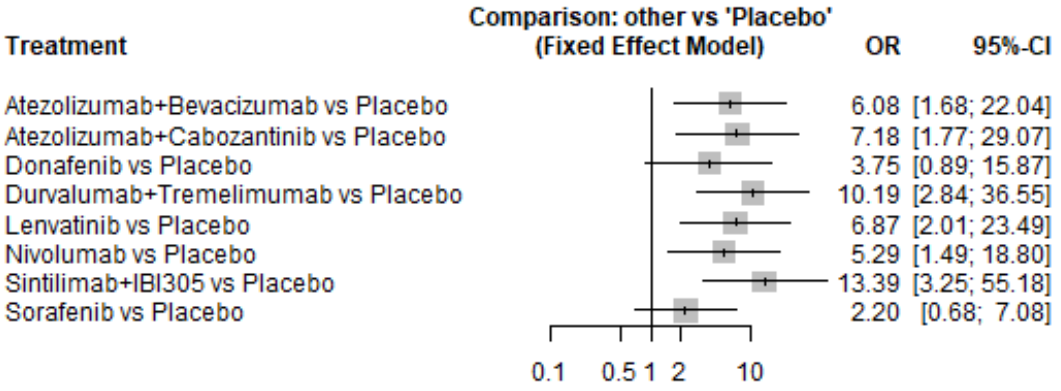
(A) Forest plot for overall survival, considering all other treatments as exposure and placebo as reference; (B) Forest plot for progression free survival, considering all other treatments as exposure and placebo as reference; (C) Forest plot for objective response rate, considering all other treatments as exposure and placebo as reference



B


Comparison: other vs 'Placebo'
Treatment
(Fixed Effect Model)
HR
95%-CI
Atezolizumab+Bevacizumab vs Placebo 0.34 [0.25; 0.46]
Atezolizumab+Cabozantinib vs Placebo 0.36 [0.26; 0.51]
Donafenib vs Placebo 0.52 [0.40; 0.68]
Durvalumab+Tremelimumab vs Placebo 0.52 [0.40; 0.67]
Lenvatinib vs Placebo 0.38 [0.30; 0.49]
Nivolumab vs Placebo 0.54 [0.41; 0.69]
Sintilimab+IBI305 vs Placebo 0.32 [0.24; 0.43]
Sorafenib vs Placebo 0.58 [0.47; 0.70]
0.5
1
2

C

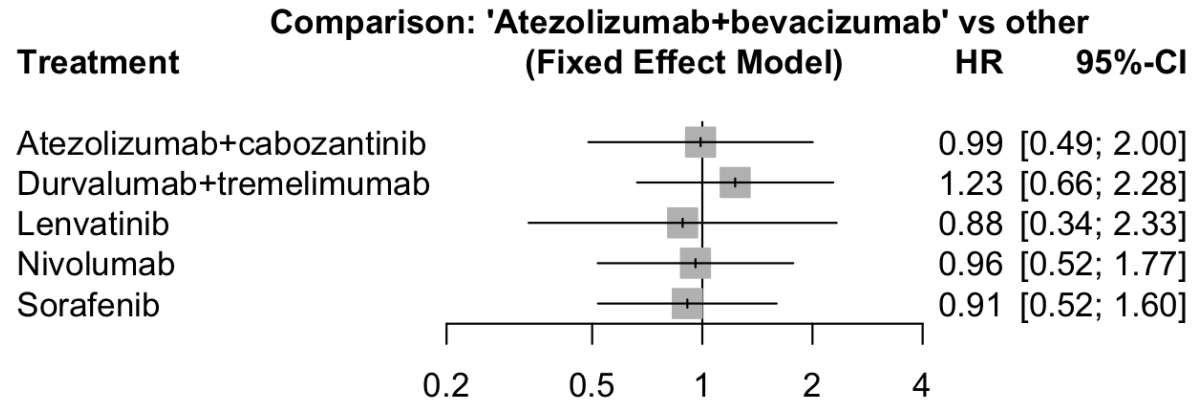

Comparison: other vs 'Placebo'
Treatment
(Fixed Effect Model)
OR
95%-CI
Atezolizumab+Bevacizumab vs Placebo 6.08 [1.68; 22.04]
Atezolizumab+Cabozantinib vs Placebo 7.18 [1.77; 29.07]
Donafenib vs Placebo 3.75 [0.89; 15.87]
Durvalumab+Tremelimumab vs Placebo 10.19 [2.84; 36.55]
Lenvatinib vs Placebo 6.87 [2.01; 23.49]
Nivolumab vs Placebo 5.29 [1.49; 18.80]
Sintilimab+IBI305 vs Placebo 13.39 [3.25; 55.18]
Sorafenib vs Placebo 2.20 [0.68; 7.08]
0.1
0.5
1
2
10

Supplementary Figure 2.

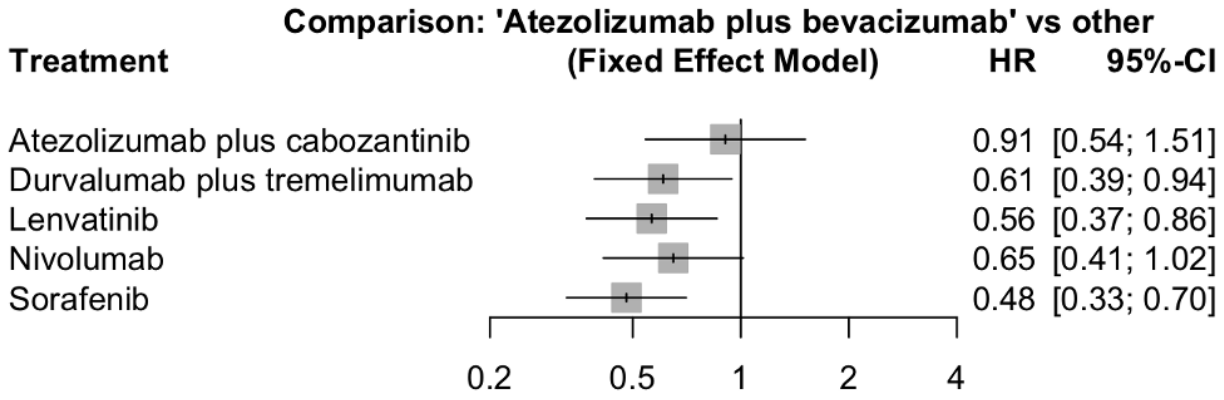
Forest plot for OS in non-viral and viral patients.

(A) Forest plot for OS considering atezolizumab plus bevacizumab as exposure and all other treatments as reference in non-viral patients; (B) Forest plot for OS considering atezolizumab plus bevacizumab as exposure and all other treatments as reference in viral patients.

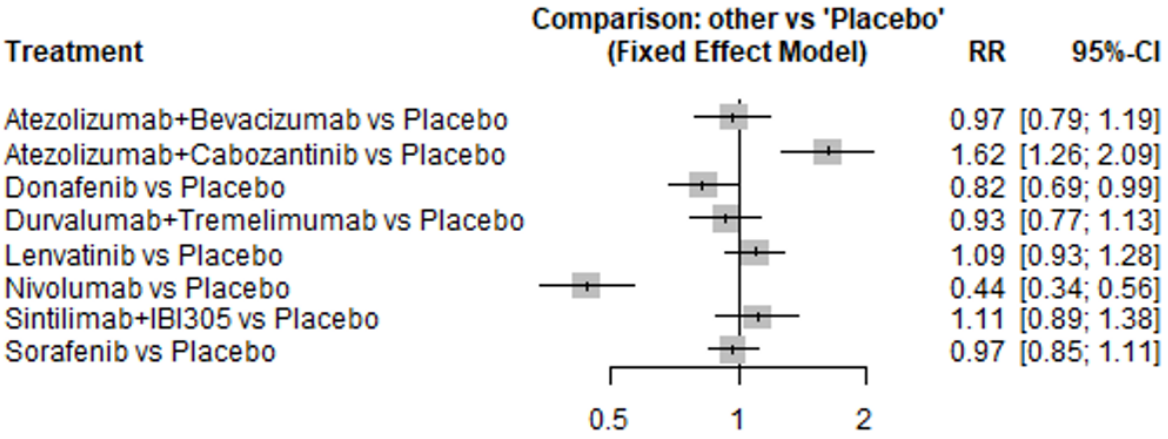
A



B



Supplementary Figure 3. Forest plot for all grade adverse events.



Supplementary Table 1. Description of the trials included in the analysis.

Name	Inclusion Criteria	Experimental arm	Control arm	Primary Endpoint (s)	Secondary Endpoint (s)	Sample size
REFLECT (non inferiority)	Advanced HCC, first line, Child A, ECOG 0-1, w/out MVI at vp4 or bile duct invasion **Stratification:** -Macrovascolar invasion and EHS or both -Region -ECOG -Body weight (<60/>60).	Lenvatinib	Sorafenib	OS (Non inf)	-PFS (superiority) -ORR (per RECIST and mRECIST by central review)	478 (lenvatinib) 476 (sorafenib)
ImBrave 150	Advanced HCC, first line, Child A, ECOG 0-1, treated varices **Stratification:** -MVI and EHS -Region -Afp -ECOG	Atezolizumab +Bevacizumab	Sorafenib	OS and PFS (coprimary)	-ORR (per RECIST and mRECIST by central review) -DOR -QoL	336 (A+B) 165 (Sor)
COSMIC	Advanced HCC, first line, Child A, ECOG 0-1 **Stratification:** **-**Region **-**MVI and EHS -Etiology (HBV-HCVother)	Atezolizumab +Cabozantinib Cabozantinib	Sorafenib	-PFS per RECIST version 1.1 by BIRC and OS (coprimary) for a+c vs sorafenib	- PFS per RECIST version 1.1 by BIRC for singleagent cabozantinib versus sorafenib.	370 (A+C) 185 (sorafenib) 185 (cabozantinib)

HIMALAYA	Advanced HCC, first line, Child A, ECOG 0-1, w/out MVI at vp4 **Stratification:** -MVI -Etiology (HBV-HCVother) -ECOG PS	Durvalumab +tremelimumab Durvalumab	Sorafenib	-OS of D+T versus sorafenib	-OS for durvalumab versus sorafenib (Non inferiority), -ORR for D+T and D alone -PFS -DOR -DCR Per RECIST, investigator review	1324 (total) 393 (D+T), 389 (D), 389 (S)

Check-Mate 459	Advanced HCC, first line, Child A, ECOG 0-1 **Stratification:** -macrovascular invasion or extrahepatic metastasis -baseline α-fetoprotein level (<400 ng/mL vs ≥400 ng/mL) -ECOG performance status (0 vs 1)	Nivolumab	Sorafenib	OS	-PFS by -ORR -per RECIST central review)	317 (nivo) 372 (sorafenib)
SHARP	Advanced HCC, first line, Child A, ECOG 0-1-2 **Stratification:** -Region -MVI or EHS(yes or no) -ECOG (0 vs 1-2)	Sorafenib	Placebo	OS and time to symptomatic progression	-time to radiological progression -DCR -Safety	299 (sorafenib) 300 (placebo)
ASIA-PACIFIC	Advanced HCC, first line, Child A, ECOG 0-1-2, in Asia **Stratification:** -Region -MVI or EHS(yes or no) -ECOG (0 vs 1-2)	Sorafenib	Placebo	OS	-time to to progression - time to symptomatic progression	150 (sorafenib) 76 (placebo)

ORIENT-32	Advanced HCC, first line, Child A, ECOG 0-1 **Stratification:** -macrovascular invasion or extrahepatic metastasis -baseline α-fetoprotein level (<400 ng/mL vs ≥400 ng/mL) -ECOG performance status (0 vs 1)	Sintilimab + IBI305	Sorafenib	OS and PFS (coprimary)		380 (sintilimab) 191 (sorafenib)
Donafenib	Advanced HCC, first line, Child A-B (7), ECOG 0-1-2, in Asia **Stratification:** -Baseline α-fetoprotein level (<400 ng/mL vs ≥400 ng/mL) -PVI or extrahepatic metastasis (yes vs no) -BCLC stage (B vs C) -Previous LRT (yes vs no)	Donafenib	Sorafenib	OS	PFS; TTP; ORR; TTF	

Supplementary Table 2. Baseline characteristics of the population included in the trials of interest

Name	Arm	Median Age	Western Region (%)	Presence Of MVI (%)	EHS (%)	Viral (%)	Child (A) (%)	ECOG 0 (%)	BCLC-C (%)
REFLECT	Lenvatinib	63	33%	23%	61%	72%	99%	64%	78%
	Sorafenib	62	33%	21%	62%	74%	99%	63%	81%
ImBrave 150	Atezo+bev	64	60%	38%	63%	70%	100%	62%	82%
	Sorafenib	66	59%	43%	56%	68%	100%	62%	81%
COSMIC	Atezo+cabo	64	72%	31%	54%	60%	100%	64%	68%
	Sorafenib	64	71%	28%	56%	61%	100%	66%	67%
HIMALAYA	Durva+Trem	65	60%	26%	53%	59%	100%	62%	80%
	Durvalumab	64	57%	24%	55%	58%	100%	61%	80%
	Sorafenib	64	60%	26%	52%	57%	100%	62%	83%
Check-Mate 459	Nivolumab	65	54%	33%	60%	54%	98%	73%	82%
	Sorafenib	65	53%	32%	56%	54%	96%	70%	78%
SHARP	Sorafenib	65	100%	36%	53%	48%	95%	54%	82%
	Placebo	66	100%	41%	50%	45%	98%	54%	83%
ASIA-PACIFIC	Sorafenib	51	NA	36%	69%	81%	97%	25%	95%
	Placebo	52		34%	68%	81%	97%	28%	96%
Orient-32	Sintilimab+ IBI 305	53	NA	28%	73%	96%	96%	48%	85%
	Sorafenib	54		26%	75%	98%	95%	48%	86%
Donafenib	Donafenib	53	NA	73%	73%	91%	99%	39%	87%
	Sorafenib	53		73%	73%	93%	96%	33%	88%

Supplementary Table 3. Tables reporting the risk of bias (high versus low) for each of the seven domains considered.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
IMbrave150	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
HIMALAYA	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
COSMIC312	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
ORIENT-32	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
CheckMate 459	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Qin et al.	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
REFLECT	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
SHARP	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Asia PACIFIC	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Reference

1. Pfister D, Nunez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature. 2021 Apr;592(7854):450-456.