Efficacy and safety of frontline systemic therapy for advanced HCC: a network meta-analysis of landmark phase III trials

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Table of contents

Supplementary Methods 1.
Search terms applied to publication databases and secondary sources.

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. exp Pembrolizumab/
24. pembrolizumab
25. exp Tislelizumab/
26. (tislelizumab or BGB-A317)
27. exp Camrelizumab/
28. (camrelizumab or AiRuiKa)
29. exp Rivoceranib/
30. (rivoceranib or apatinib)
31. exp Sunitinib/
32. (sunitinib or Sutent or SU11248)
33. exp Brivanib/
34. (Brivanib or Brivanib alaninate or BMS582664)
35. exp Linifanib/
36. (linifanib or ABT869)
37. 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 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. randomized controlled trial.pt.
39. controlled clinical trial.pt.
40. randomi#ed.ab.
41. placebo.ab.
42. randomly.ab.
43. clinical trials as topic.sh.
44. trial.ti.
45. 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 4 and 37 and 45

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 and data analysis.

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 class 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 or AEs of grade 3 or higher 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.

A frequentist network meta-analysis using (i) sorafenib and (ii) atezolizumab plus bevacizumab as the comparator was performed to compare (a) the efficacy (OS, PFS, ORR and DCR) as well as (b) the safety (all grade AE, and grade ≥3 AEs) of different treatment options. Data on ORR, DCR and AEs extracted from the studies were considered to calculate odds ratios (ORs) and relative risks (RRs) as well as corresponding 95% confidence intervals (CIs) for the association between treatment regimens and radiological response or the occurrence of AEs, respectively. Fixed effect multivariable meta-regression models were performed to estimate the indirect hazard HRs, ORs or RRs and respective 95% CIs. Two analyses were performed to evaluate efficacy: the first compared the efficacy of sorafenib with all other treatment options as sorafenib was the gold-standard comparator for most of the included trials; the second analysis evaluated the efficacy of atezolizumab plus bevacizumab, the current standard of care, against all other treatment options. For safety, the incidence of AEs (all grade AE, and grade ≥3 AEs) was compared to sorafenib. Forest plots were generated to graphically demonstrate the comparisons of interest ranking treatments according to their HRs. P-scores for efficacy (OS and PFS) were reported. P-scores are a measure reflecting the extent of certainty that a treatment is better than another one, averaged over all competing therapies.

Fig. S1. Forest plot, HR and corresponding confidence intervals for the association between atezolizumab plus bevacizumab and mortality considering each other treatment as reference.

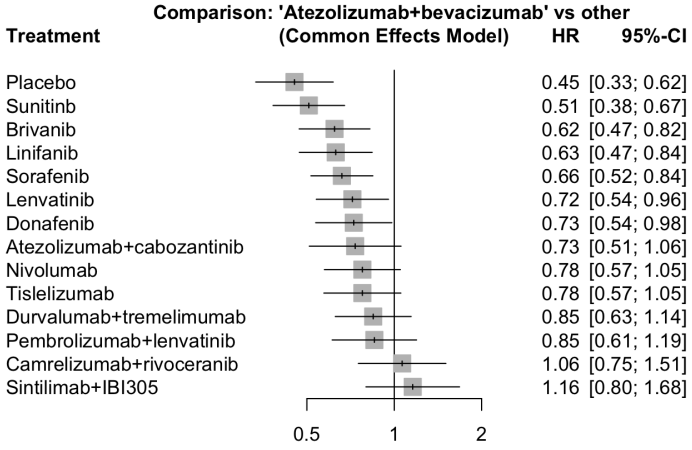


Fig. S2. Forest plot, HR and corresponding confidence intervals for the association between atezolizumab plus bevacizumab and progression considering each other treatment as reference.

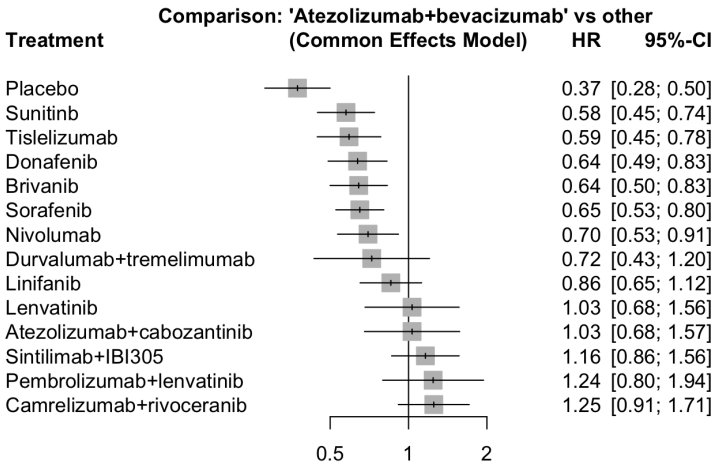


Fig. S3. Forest plot, HR and corresponding confidence intervals for the association between Sorafenib and mortality considering Sorafenib as reference in HBV patients.

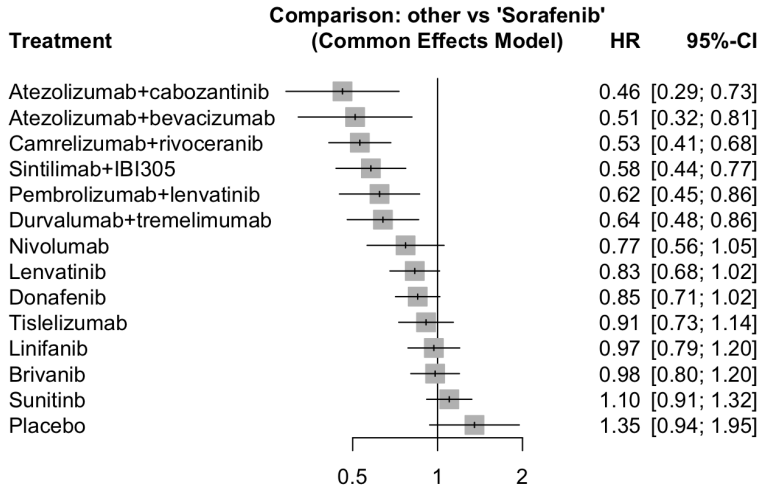


Fig. S4. Forest plot, HR and corresponding confidence intervals for the association between Sorafenib and mortality considering Sorafenib as reference in HCV patients.

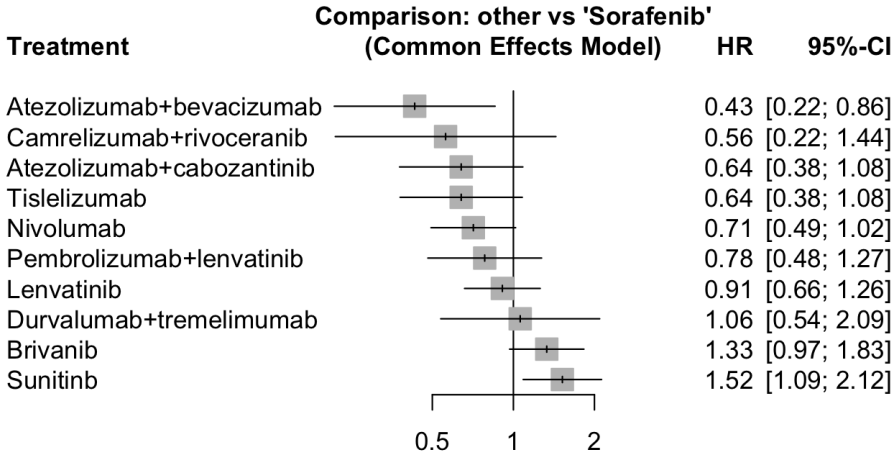


Fig. S5. Forest plot, HR and corresponding confidence intervals for the association between Sorafenib and mortality considering Sorafenib as reference in non-viral patients.

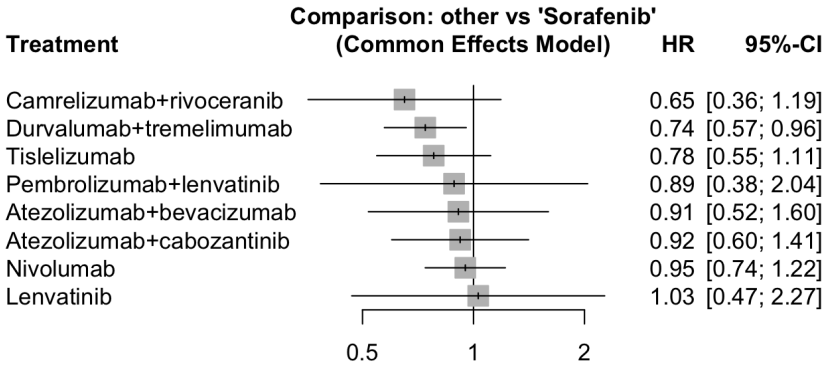
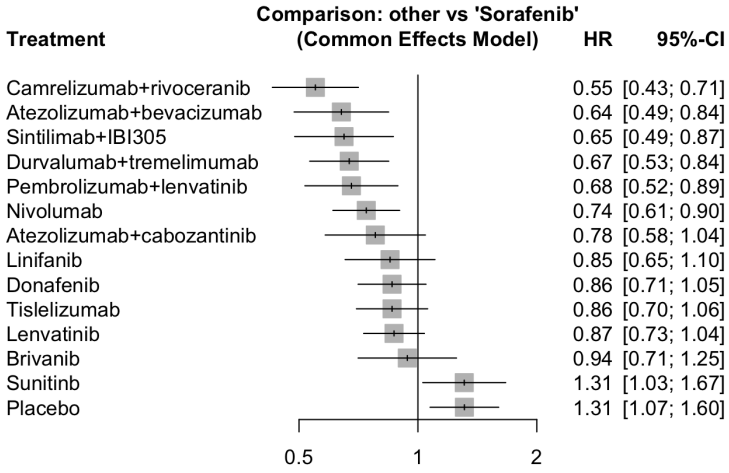


Fig. S6. Forest plot, HR and corresponding confidence intervals for the association between Sorafenib and mortality considering Sorafenib as reference in patients with EHS and/or MVI



*For Sunitinib, the HR was available only for patients with macro-vascular invasion

Table S1.
Description of the trials included in the analysis.

Name	Inclusion Criteria	Experimental arm	Control arm	Primary Endpoint (s)	Secondary Endpoint (s)	Sample size
Johnson P. et al., 2013	Advanced HCC, first-line, Child A, ECOG PS 0 or 1, , w/out MVI at vp4 **Stratifications**: -ECOG PS 0 or 1 -EHS +/- MVI -Region	Brivanib	Sorafenib	OS (non-inferiority)	TTP; ORR; DCR; safety	577 (Bri), 578 (Sor) [ITT]
Cheng A. et al., 2013	Advanced or metastatic HCC, Child A, ECOG PS 0-1 **Stratifications**: -Region -Prior TACE -MVI, EHS	Sunitinib	Sorafenib	OS	PFS; TTP, safety	530 (Sun), 544 (Sor)
Cainap C. et al., 2015	Advanced HCC, first-line, Child A, ECOG 0 or 1 **Stratifications:** -Region (Outside Asia, Japan and rest of Asia) -ECOG PS 0 or 1 -MVI, EHS -HBV (yes or no)	Linifanib	Sorafenib	OS (both superiority and non-inferiority)	TTP; ORR	514 (Lin), 521 (Sor) [ITT]
REFLECT	Advanced HCC, first line, Child A, ECOG 0-1, w/out MVI at vp4 or bile duct invasion **Stratification:** -MVI and EHS or both -Region -ECOG -Body weight (<60/>60).	Lenvatinib	Sorafenib	OS (Non-inferiority)	-PFS (superiority) -ORR (per RECIST and mRECIST by central review)	478 (lenvatinib) 476 (sorafenib)
IMbrave150	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-312	Advanced HCC, first line, Child A, ECOG 0-1 **Stratification:**	Atezolizumab +Cabozantinib Cabozantinib	Sorafenib	PFS per RECIST version 1.1 by BIRC	- PFS per RECIST version 1.1 by BIRC for single-agent	370 (A+C) 185 (sorafenib)

	-Region -MVI and EHS -Etiology (HBV-HCV-other)			and OS (coprimary) for a+c vs sorafenib	cabozantinib versus sorafenib.	185 (cabozantinib)
HIMALAYA	Advanced HCC, first line, Child A, ECOG 0-1, w/out MVI at vp4 **Stratification:** -MVI -Etiology (HBV-HCV-other) -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:** -MVI or extrahepatic metastasis -baseline α-fetoprotein level (<400 ng/mL vs ≥400 ng/mL) -ECOG performance status (0 vs 1)	Nivolumab	Sorafenib	OS	-PFS -ORR -per RECIST by 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, w/out MVI at vp4 **Stratification:** -MVI or extrahepatic metastasis -baseline α-fetoprotein level (<400 ng/mL vs ≥400 ng/mL)	Sintilimab + IBI305	Sorafenib	OS and PFS (coprimary)		380 (sintilimab) 191 (sorafenib)

	-ECOG performance status (0 vs 1)					
Qin S. et al., 2021	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) -MVI or extrahepatic metastasis (yes vs no) -BCLC stage (B vs C) -Previous LRT (yes vs no)	Donafenib	Sorafenib	OS	PFS; TTP; ORR; TTF	334 (don) 334 (sor)
LEAP-002	Advanced HCC, first-line, Child A, ECOG 0-1, w/out MVI at vp4 or bile duct invasion **Stratification:** -Baseline α-fetoprotein level (<400 ng/mL vs ≥400 ng/mL) -MVI or extrahepatic metastasis (yes vs no) -ECOG PS (0 vs 1) -Region	Lenvatinib + Pembrolizumab	Lenvatinib + placebo	OS and PFS (coprimary)	ORR and DOR per RECIST v1.1 and mRECIST by BICR Safety/tolerability	395 (Len/Pembro) 399 (Len/placebo)
Qin S. et al., 2022	Advanced HCC, first-line, Child A, ECOG 0 or 1 **Stratifications**: -MVI and/or EHS (yes or no) -Region - Baseline α-fetoprotein level (<400 ng/mL vs ≥400 ng/mL)	Camrelizumab + rivoceranib	Sorafenib	OS and PFS (coprimary)	ORR by RECIST 1.1	272 (Cam/Rivo) 271 (Sorafenib)
RATIONALE 301	Advanced HCC, first-line, Child A, ECOG 0 or 1, w/out thrombus MVI at Vp4 or IVC **Stratifications**: -MVI, EHS -ECOG PS -Aetiology (HCV vs other (inc HBV) -Region (Asia vs Japan + Rest of the world)	Tislelizumab	Sorafenib	OS (non-inferiority)	ORR; PFS; DOR, safety	342 (Tis), 332 (Sor)

Table S2. Risk of bias assessment according to the Cochrane risk of bias assessment tool

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cheng A. et al., 2013	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Johnson P. et al., 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cainap C. et al., 2015	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
REFLECT	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
IMbrave150	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
COSMIC-312	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
CheckMate-459	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
ORIENT-32	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Qin et al. 2021	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
LEAP-002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Qin S. et al., 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
RATIONALE 301	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table S3. P-scores reporting the probability for each treatment of being the best in reducing the risk of death.

Treatment	p-score
Sintilimab+IBI305	0.9530
Camrelizumab+rivoceranib	0.9091
Atezolizumab+bevacizumab	0.8632
Pembrolizumab+lenvatinib	0.7100
Durvalumab+tremelimumab	0.7016
Nivolumab	0.5772
Tislelizumab	0.5765
Atezolizumab+cabozantinib	0.4815
Donafenib	0.4660
Lenvatinib	0.4428
Sorafenib	0.2946
Linifanib	0.2329
Brivanib	0.2158
Sunitinb	0.0632
Placebo	0.0127

Table S4. P-scores reporting the probability for each treatment of being the best in reducing the risk of PFS events.

Treatment	p-score
Camrelizumab+rivoceranib	0.9075
Pembrolizumab+lenvatinib	0.8993
Sintilimab+IBI305	0.8508
Atezolizumab+cabozantinib	0.7452
Lenvatinib	0.7287
Atezolizumab+bevacizumab	0.7184
Linifanib	0.5882
Durvalumab+tremelimumab	0.4201
Nivolumab	0.4142
Sorafenib	0.3214
Brivanib	0.2993
Donafenib	0.2837
Tislelizumab	0.1831
Sunitinb	0.1398
Placebo	0.0004