AN UMBRELLA REVIEW ON THE **EFFECTIVENESS OF SYSTEMATIC TREATMENTS FOR THE MANAGEMENT OF ADVANCED HEPATOCELLULAR CARCINOMA** (HCC)

Zile I[1], Rabar S[1], McCormick E[1], Bem D[1]
[1] Health Economics and Outcomes Research Ltd, Cardiff, UK.

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Introduction

- HCC is the sixth most common cancer worldwide and the third most common cause of cancer-related death[1] with most cases of HCC to be diagnosed at a more advanced stage.
- Despite improvements in survival for patients with advanced HCC, prognosis remains poor and existing treatment options are associated with a range of unpleasant side-effects.
- This umbrella review aims to determine:
  - What is the clinical efficacy and safety of systemic therapies used in patients with advanced HCC?
  - What is the quality of the available evidence?

Methods

- The review protocol is registered with PROSPERO (CRD42021259210).
- Searches were conducted in Ovid MEDLINE, Ovid Embase, Cochrane Database of Systematic Reviews, DARE and Epistimonikos from January 2011 until May 2021.
- Systematic reviews and meta-analyses of randomised controlled trials examining systemic treatments (alone or in combination with other systemic or locoregional therapies) for adults diagnosed with advanced HCC were eligible for inclusion.
- Screening was conducted by two independent reviewers with discrepancies resolved by discussion or the involvement of a third reviewer.
- Data extraction was performed by a single reviewer and checked by a second reviewer.
- Outcomes of interest included overall survival, progression-free survival, response rate and serious adverse events.
- The Assessment of Multiple Systematic Reviews (AMSTAR2) tool[2] was used to assess risk of bias in the included reviews.

Figure 1: PRISMA diagram of included studies

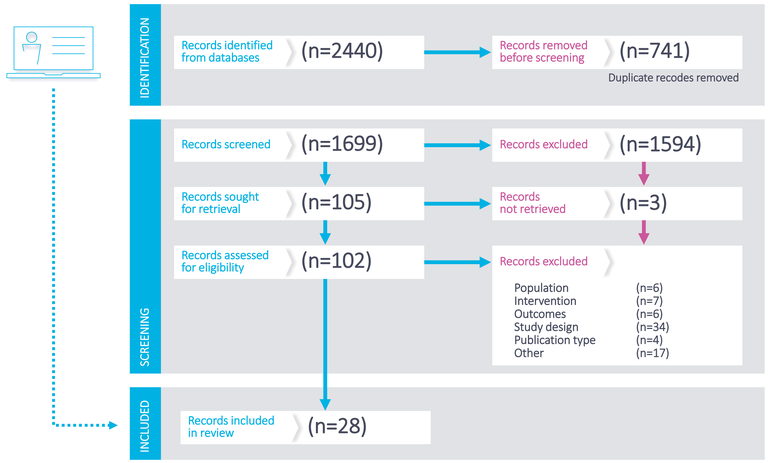


Table 1: Summary of included systematic reviews and meta-analyses

AUTHOR, YEAR	NO. OF TRIALS* (COHORT SIZE)	INTERVENTION	COMPARATOR	TREATMENT LINE
Zhang, 2010	3 (924)	SOR	PBO	Any
Ji, 2011	9 (759)	Octreotide	PBO/ BSC	Any
Shen, 2013	4 (725)	SOR	PBO	Any
Shao, 2015	4 (1491)	SOR	PBO/SU/BRIV	1st
Niu, 2016	11 (6594)	SOR+/- ERL, RAM, EVE, BRIV, TIV, SU	PBO	Any
Roviello, 2016	5 (1815)	AXI, BRIV, TIV, EVE, RAM	PBO	2nd
Cucchetti, 2017	6 (4812)	SOR +/- ERL, LIN, BRIV, SU	PBO	1st
Kim, 2017	6 (2388)	BRIV, TIV, EVE, AXI, RAM, REG	PBO	2nd
Wang, 2018	6 (5037)	SU, BRIV, LIN, LEN, SIRT	SOR	Any
Bakouny, 2019	13 (5076)	RAM, TIV, ADI-PEG 20, CAB, REG, S-1, COD, AXI, EVE, BRIV	PBO	2nd
Cabibbo, 2019	10 (3429)	SOR	PBO	1st
Ding, 2020	20 (9288)	BEV + ERL, BRIV, DOV, LEN, LIN, NIN, ORA, SU, VAN, SOR +/- TIG, EVE, ERL	PBO	1st
Santos, 2020	2 (1280)	CAB, REG	PBO	2nd
Venerito, 2020	3 (933)	SIRT	SOR	1st
Oranratnachai, 2021	19 (7846)	DXR, NOLA, PIAF, FOLFOX4, SU, BRIV, LIN, DOV, LEN, NIN, BEV + ERL, SOR +/- DXR, ERL, EVE	NR	1st
Parikh, 2021	3 (191)	NIVO + IPI	CAB, REG, NIVO, PBO	2nd
Park, 2021	24 (12947)	ATEZO + BEV, DON, NIVO, LEN, LIN, BRIV, SU, SOR +/- ERL, RES, TIG, DXR	SOR (1L), PBO (2L)	1st, 2nd
Pollock, 2021	3 (NR)	Y-90 resin microspheres	SOR	1st

ATEZO: atezolizumab; AXI: axitinib; BEV: bevacizumab; BRIV: brivanib; CAB: cabozantinib; CAPE: capecitabine; COD: codrituzumab; DON: donafenib; DOV: dovitinib; DOV: dovitinib; DXR: doxorubicin; ERL: erlotinib; EVE: everolimus; IPI: ipilimumab; LEN: Lenvatinib; LIN: linifanib; NIN: nintedanib; NIVO: nivolumab; NOLA: nolatrexed ORA: orantinib; PBO: placebo; PEM: pembrolizumab; RAM: ramucirumab; RES: resminostat; REG: regorafenib; SOR: sorafenib; SU: sunitinib; TIG: tigatuzumab; TIV: tivatinib; VAN: vandetanib.

* Number of trials included in meta-analyses

Table 2: Median HR for OS of interventions and comparators

TREATMENT ARMS	No. of SLRs reporting	OS HR (range)	Statistical significance
First line			
Sorafenib vs Placebo	2	0.68-0.73	Yes
Sorafenib combinations vs Sorafenib	2	0.93-1.05	No
Atezolizumab + Bevacizumab vs Sorafenib	1	0.58	Yes
Lenvatinib vs Sorafenib	1	0.92	No
Donafenib vs Sorafenib	1	0.83	Yes
Second line			
Cabozantinib vs Placebo	1	0.76	Yes
Regorafenib vs Placebo	1	0.63	Yes
Nivolumab + Ipilimumab vs Placebo	1	0.35	Yes
Nivolumab + Ipilimumab vs Nivolumab	1	0.58	Yes
Nivolumab + Ipilimumab vs Cabozantinib	1	0.46	Yes
Nivolumab + Ipilimumab vs Regorafenib	1	0.56	Yes

All other interventions not superior to placebo or those presented. HR: hazard ratio; OS: overall survival.

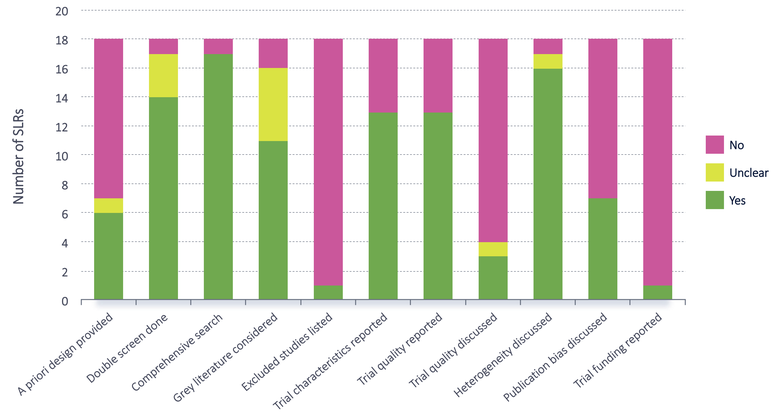
Results

- The searches yielded 1,699 records, of which 28 were considered relevant for inclusion.
- 10 studies did not report any pooled hazard ratios (HRs) for overall survival and are not presented here. The remaining 18 studies are summarized in Table 1.
- Pooled HRs for overall survival are reported in Table 2.

Risk of Bias assessment

- Few reviews reported an a priori design in their methods.
- Hardly any reviews provided lists of excluded studies or described conflicts of interest in the individual studies they included.
- Conversely, almost all studies conducted comprehensive database searches, used double screening and considered the heterogeneity of included studies.

Figure 2: Results of the risk of bias assessment based on the AMSTAR2 checklist



Conclusions

- Sorafenib combination therapy is non-inferior to sorafenib monotherapy.
- Donafenib and the combination of atezolizumab + bevacizumab show superiority to sorafenib for OS.
- The OS with all other interventions, including the NICE approved lenvatinib, is non-inferior to sorafenib.
- Nivolumab + ipilimumab shows a survival benefit over cabozantinib, regorafenib and nivolumab monotherapy as 2-nd line therapy for advanced HCC.
- The published SLRs are generally of good quality, though many fail to report full details on their methods and included studies

References
1. Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. J Carcinog. 2017;16:1.
2. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358.

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