A Systematic Literature Review of Patient-Reported Outcomes in Phase III Randomized Controlled Trials of Hepatocellular Carcinoma in a First-Line Setting

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Conclusion

- Treatment of advanced HCC requires consideration of health-related quality of life (HRQoL). First-line systematic therapies may delay functional decline in advanced HCC by improving HRQoL in clinically relevant domains compared with sorafenib

Background

- Hepatocellular carcinoma (HCC) is a leading cause of death and is associated with significant morbidity
- Patient-reported outcomes (PROs) provide insights into the patient's subjective experience with disease and treatment

Objective

To evaluate the PROs results among the advanced HCC patients treated with first-line systemic therapy

Methodology

- This review adhered to NICE and PRISMA guidelines for systematic literature reviews (SLRs), following standard methodology with transparent, reproducible, and unbiased approach
- EMBASE® and MEDLINE® were searched for English language articles published from inception to December 2022 for randomized controlled trials (RCTs) evaluating PROs in advanced HCC
- Figure 1 presented the pre-defined PICOS criteria for study selection

Population
Advanced HCC patients (age ≥18 years) treated with first-line systemic therapy

Intervention and Comparator
Pharmacotherapy, Placebo, Best supportive care (BSC)

Outcomes
Patient-Reported Outcomes (PROs)

Study design
Randomized Controlled Trials (RCTs)

Figure 1: Prespecified PICOS eligibility criteria for selection of evidence

- The risk of bias assessment was performed using Cochrane's RoB-2 tool
- Meta-analysis was conducted in accordance with the recommendations of the Cochrane Library and ISPOR Task Force
- Network meta-analysis (NMA) used generalized linear models with fixed effects within a Bayesian framework

Results

- Four RCTs i.e., IMbrave150, REFLECT, CheckMate 459, and HIMALAYA met the eligibility criteria. Table 1 provides the summary of study characteristics
- **Interventions**: atezolizumab + bevacizumab, tremelimumab + durvalumab (STRIDE regimen), lenvatinib, nivolumab, durvalumab and sorafenib

Table 1: Characteristics of the included RCTs

Parameters	IMbrave150	REFLECT	CheckMate 459	HIMALAYA
Phase III	✓	✓	✓	✓
Blinding (Open-label)	✓	✓	✓	✓
Global (Multiple countries)	✓	✓	✓	✓
EORTC-QLQ C30	✓	✓	✗	✓
EQ-5D VAS	✗	✓	✗	✗
EQ-5D index	✗	✓	✗	✗
EORTC QLQ-HCC18	✓	✓	✗	✓
FACT-Hep	✗	✗	✓	✗

- Participant's mean age ranged from 61.3 to 65.0 years. Most were Asian males with ECOG PS 0 and advanced BCLC stage C (Figure 2)

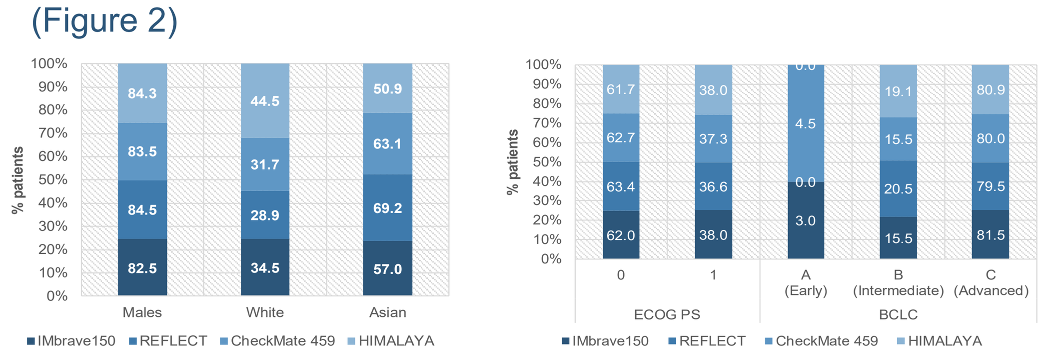

Figure 2: Population characteristics across included RCTs

- **LEN, STRIDE regimen, and ATZ + BEV vs. SORA**: Reduction in the risk of deterioration on EORTC QLQ-C30 generic cancer symptom scales such as fatigue, pain, diarrhea, appetite loss, nausea, and vomiting (Figure 3)
- **ATZ + BEV vs. SORA**: Reduction in the risk of deterioration on symptom scales (dyspnoea and insomnia) and functioning (emotional, social, and cognitive). Further, ATZ + BEV, and lenvatinib reduced the risk of deterioration on disease-symptom scales (body image and nutrition) (Figure 3)
- **ATZ + BEV vs. SORA**: Reduction in the risk of deterioration on the HCC18 disease-specific symptom scales (fatigue, pain, abdominal swelling) (Figure 3)
- **NIVO vs. SORA**: Reduction in the risk of deterioration on all disease-specific functioning and symptom scales of FACT-Hep (Figure 4)

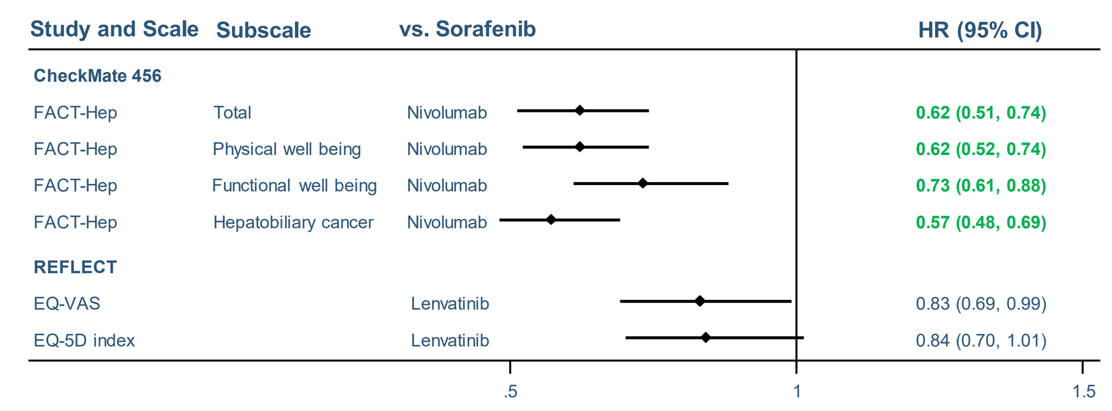

Figure 4: Hazard ratio for time to symptom deterioration assessed via FACT-HEP, EQ -5D VAS, EQ-5D index across included studies

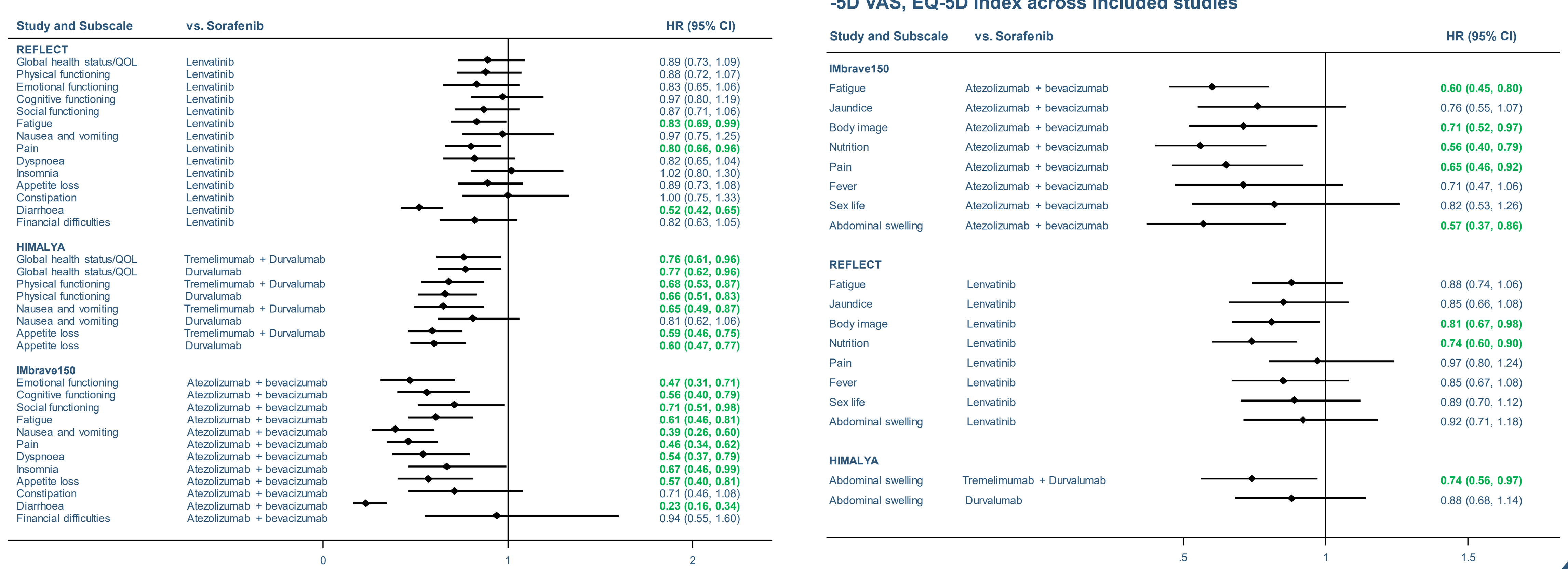

Figure 3: Hazard ratio for time to symptom deterioration assessed via EORTC QLQ-C30 (left) and EORTC QLQ-HCC 18 (right) across included studies

EORTC-HCC 18: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma 18-question module; EORTC-QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D VAS: EuroQoL 5 Dimensions Visual Analogue Scale; FACT-Hep: Functional Assessment of Cancer Therapy – Hepatobiliary; **Subscales not differentiated

Results (Cont'd)

- The direct meta-analysis statistically significantly favoured targeted therapy (atezolizumab + bevacizumab, STRIDE regimen, lenvatinib, durvalumab) vs. sorafenib in 14 of 22 symptoms (green highlighted in Figure 5)
- In the NMA, all evaluated treatments showed numerically better results compared to sorafenib for nausea and vomiting, appetite loss, and abdominal swelling symptoms

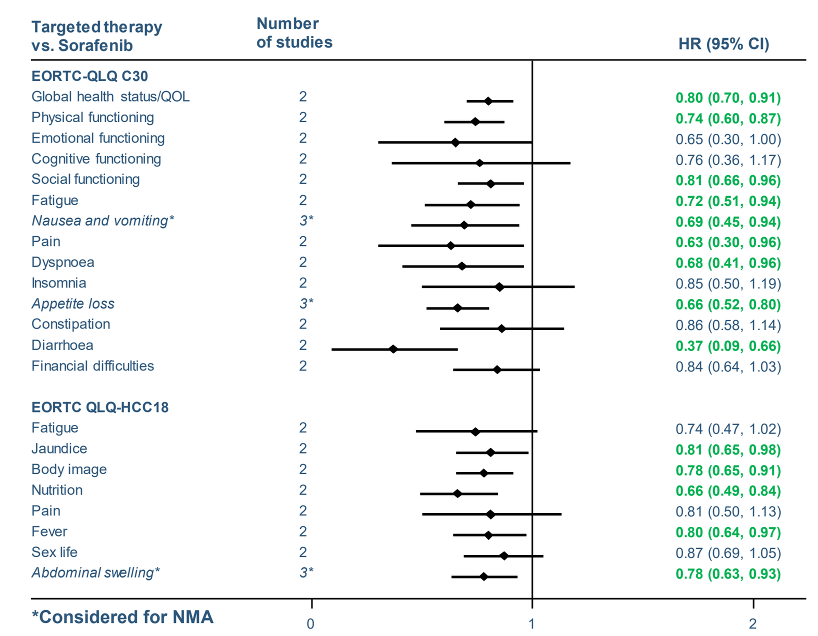

Figure 5: Forest plot of comparison between targeted therapy vs. sorafenib (Random-effects model)

Table 2: League tables with NMA estimates for symptoms sub-scales of *EORTC QLQ-C30/**HCC-18 (Fixed-effects model)

Appetite loss*	SORA	ATZ + BEV	LEN	STRIDE regimen	DURV
SORA	1	0.57 (0.4, 0.81)	0.89 (0.73, 1.08)	0.59 (0.46, 0.75)	0.6 (0.47, 0.77)
ATZ + BEV	1.75 (1.23, 2.5)	1	1.56 (1.04, 2.34)	1.04 (0.67, 1.59)	1.05 (0.68, 1.62)
LEN	1.12 (0.92, 1.37)	0.64 (0.43, 0.96)	1	0.66 (0.48, 0.91)	0.67 (0.49, 0.92)
STRIDE regimen	1.7 (1.33, 2.17)	0.97 (0.63, 1.49)	1.51 (1.1, 2.07)	1	1.02 (0.72, 1.44)
DURV	1.67 (1.3, 2.13)	0.95 (0.62, 1.46)	1.48 (1.08, 2.03)	0.98 (0.69, 1.39)	1
Nausea and vomiting*	**SORA**	**ATZ + BEV**	**LEN**	**STRIDE regimen**	**DURV**
SORA	1	0.39 (0.26, 0.59)	0.97 (0.75, 1.25)	0.65 (0.49, 0.86)	0.81 (0.62, 1.06)
ATZ + BEV	2.56 (1.69, 3.89)	1	2.49 (1.52, 4.06)	1.67 (1, 2.77)	2.08 (1.26, 3.41)
LEN	1.03 (0.8, 1.33)	0.4 (0.25, 0.66)	1	0.67 (0.46, 0.98)	0.84 (0.58, 1.21)
STRIDE regimen	1.54 (1.16, 2.05)	0.6 (0.36, 1)	1.49 (1.02, 2.2)	1	1.25 (0.84, 1.85)
DURV	1.23 (0.94, 1.61)	0.48 (0.29, 0.79)	1.2 (0.83, 1.74)	0.8 (0.54, 1.19)	1
Abdominal swelling**	**SORA**	**ATZ + BEV**	**LEN**	**STRIDE regimen**	**DURV**
SORA	1	0.57 (0.37, 0.87)	0.92 (0.71, 1.19)	0.74 (0.56, 0.97)	0.88 (0.68, 1.14)
ATZ + BEV	1.75 (1.15, 2.67)	1	1.61 (0.99, 2.64)	1.3 (0.78, 2.15)	1.55 (0.94, 2.53)
LEN	1.09 (0.84, 1.4)	0.62 (0.38, 1.01)	1	0.8 (0.55, 1.17)	0.96 (0.67, 1.37)
STRIDE regimen	1.35 (1.03, 1.78)	0.77 (0.47, 1.28)	1.24 (0.86, 1.81)	1	1.19 (0.82, 1.73)
DURV	1.14 (0.88, 1.47)	0.65 (0.4, 1.06)	1.05 (0.73, 1.5)	0.84 (0.58, 1.22)	1

Based on residual deviance and DIC statistics, the simpler fixed-effects model was preferred over a complex random-effects model for parsimony and interpretability

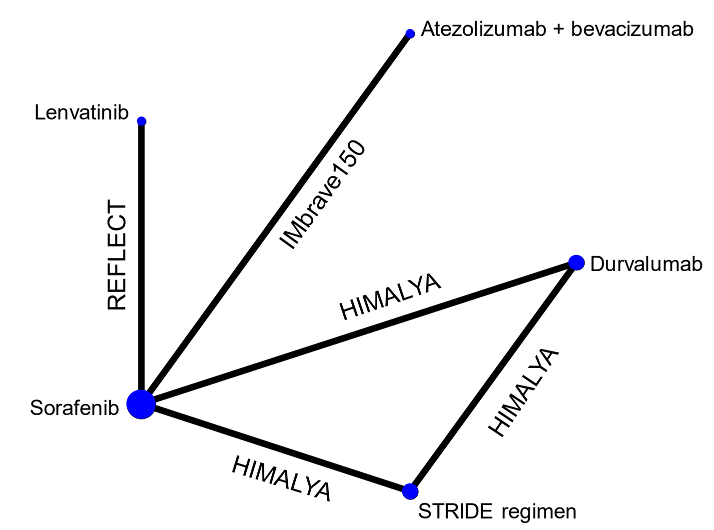

Figure 6: Network diagram for time to symptom deterioration

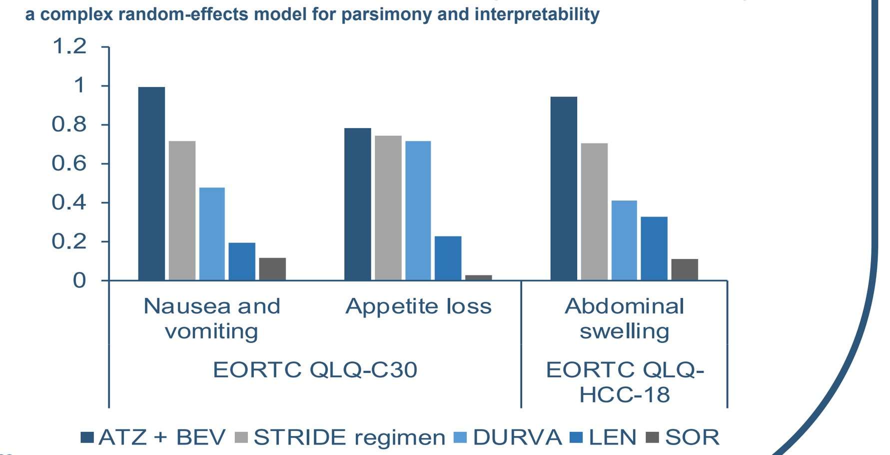

Figure 7: SUCRA plot to rank interventions

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Sponsorship

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