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ORIGINAL RESEARCH

Profile of lenvatinib in the treatment of hepatocellular carcinoma: design, development, potential place in therapy and network meta-analysis of hepatitis B and hepatitis C in all Phase III trials

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Purpose: Sorafenib is the only approved drug in first-line treatment for hepatocellular carcinoma. Recently, the Phase III REFLECT trial proved lenvatinib not inferior to sorafenib, potentially establishing a new standard of care in this setting. The study showed that both have similar overall survivals, yet with longer time to progression for lenvatinib. Currently, the selection of one or other is not based on clinical or biological parameters for this reason we performed a network meta-analysis and we also analyzed the REFLECT trial and its implications in the current and future clinical practice.

Materials and methods: We performed the meta-analysis according to the Prisma statement recommendations. HR was the measure of association for time to progression and overall survival. The pooled analysis of HR was performed using a random effect model, fixing a 5% error as index of statistical significance.

Results: For HBV-positive patients, there was a clear trend in favor of lenvatinib over sorafenib (HR 0.82 95% credible interval [CrI] 0.60–1.15). For HCV-positive no differences between lenvatinib and sorafenib were observed (HR 0.91 95% CrI 0.41–2.01). The data showed that lenvatinib could be the best drug for HBV-positive patients in 59% of cases compared to only 1% of patients treated with sorafenib.

Conclusion: The identification of clinical or biological markers that could predict response or resistance to treatments is needed to guide treatment decision. This network meta-analysis demonstrates that the etiology is a good candidate and this result should be validated in a specific trial.

Keywords: sorafenib, hepatocellular carcinoma, randomized trial, biomarkers, erlotinib, linifanib, sunitinib, brivanib

Introduction

Sorafenib was approved thank to two positive trials, the SHARP study in 2007[1] and the Asia Pacific study in 2008.[2] However, clinical trials investigating sunitinib,[3] brivanib,[4] and linifanib[5] as first-line treatments, with sorafenib as a control arm, failed to meet their primary endpoint of improving overall survival (OS). Sorafenib is the only systemic drug approved in this setting of patients. Lenvatinib represents an alternative molecular-targeted therapy option for hepatocellular carcinoma (HCC) patients.[6] It is an oral multireceptor tyrosine kinase inhibitor (TKI) of the activities of the vascular endothelial growth factor (VEGF) receptors (VEGFR1,

VEGFR2, and VEGFR3), the fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3, and FGFR4) and the alpha and beta platelet-derived growth factor receptors.[7–10]

The VEGF-signaling pathway is the key regulator of tumor growth and metastasis;[11] VEGFR2 induces major phenotypic changes of endothelial cells in angiogenesis, including proliferation, migration, survival, and tube formation.[12]

The most important difference between this drug and other TKIs, especially sorafenib, is the ability to potently inhibit FGFRs. The FGFR signaling pathway plays an important role in diverse cell functions, including proliferation, differentiation, apoptosis, and migration, and also in tumor proliferation, angiogenesis, migration, and survival.[13-15]FGFR pathway could be subject to various somatic aberrations, such as gene amplification, point mutations, translocations, and isoform switching, resulting in carcinogenesis.[16,17]In vivo, lenvatinib shows a more potent anti-tumor activity than in vitro.[18,19]

Preliminary evidence[20] of tumor shrinkage in HCC patients resulted in the design of a single-arm, open-label, multicenter Phase II trial[21] evaluating lenvatinib in patients with advanced HCC. In this trial, 46 patients were enrolled at 14 sites across Japan and Korea to receive lenvatinib. As for the primary endpoint, a median TTP of 7.4 months (95% CI 5.5–9.4) was obtained. The study showed a 37% ORR and a stable disease in 41% of patients with a 78% disease control rate (mRECIST criteria). Median OS was 18.7 months (95% CI 12.7–25.1).

Following the results of the Phase II trial, a randomized, open-label Phase III trial was designed[6] with the aim to determine whether lenvatinib was not inferior to sorafenib in advanced HCC in term of OS. The non-inferiority margin was set at 1.08. A total of 954 patients were randomly assigned to receive either lenvatinib (n=478) or sorafenib (n=476). A median OS of 13.6 months (95% CI 12.1–14.9) and 12.3 months (95% CI 10.4–13.9) was reached in the lenvatinib arm and the sorafenib arm, respectively, with a HR)of 0.92 (95% CI 0.79–1.06), thus meeting the criteria for non-inferiority. The secondary endpoint of progression-free survival (PFS) of 7.4 months (95% CI 6.9–8.8) and 3.7 months (95% CI 3.6–4.6) was in favor of the lenvatinib arm (HR 0.66 $P<0.0001$). Similarly, the lenvatinib arm showed better ORR than the sorafenib arm (mRECIST criteria), with ORR of 24.1% (20.2–27.9) and 9.2% (6.6–11.8), respectively (OR 3.13 $P<0.0001$).

The lenvatinib arm and the sorafenib arm showed different toxicity profiles. The most common any-grade advserse events (AEs) for lenvatinib were hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased weight (13%), whereas palmar-plantar erythrodysesthesia (52%), diarrhea (46%), hypertension (30%), and decreased appetite (27%) for sorafenib. Treatment-related grade ≥3 AEs were observed in 57% and 49% of patients in the lenvatinib arm and in the sorafenib arm, respectively. Similarly, serious treatment-related AEs were more frequent in the lenvatinib arm with an incidence of 18% vs 10% in the sorafenib arm.

Actually the indication of Lenvatinib and Sorafenib are in first line in patients with advanced hepatocellular carcinoma. Currently, the selection of one or other is not based on clinical or biological parameters.

To date, there are no validated prognostic nor predictive markers of response to sorafenib in HCC, although hepatitis status seems to be a potential candidate.

In the subgroup analysis of the SHARP study[1], sorafenib showed an advantage in term of OS on subgroup of patients positive for HCV (0.50; 95% CI 0.32-0.77), differently no different was observed in HBV-positive patients (0.76; 95% CI 0.38–1.50, P=not significant). The same results were obtained for TTP (HR =1.03 and 0.43 for HBV-positive and HCV-positive patients, respectively). These data were confirmed in the Asia-Pacific trial. In the pooled analysis of the SHARP and Asia- Pacific trials, Bruix et al confirmed that the absence of HCV was a potential prognostic factor for poorer OS (HR 0.7, P=0.02). The authors revealed that HBV-positive patients did not show a significant difference in treatment response compared to HBV-negative patients (HR =0.78; 95% CI 0.57–1.06) and OS (HR =1.128, P=0.4538).

A recent meta-analysis by Jackson et al[22] highlighted that the benefit in OS depends on the patient's status of hepatitis. OS improves in HBV-negative and HCV-positive patients when treated with sorafenib. However, as recently pointed out by Personeni et al,[23] Jackson et al only considered negative data from randomized trials comparing sorafenib with other drugs (brivanib,[4] linifanib[5], and sunitinib[3]), disregarding both the SHARP[1] and the Asia-Pacific[2] trials that evaluated sorafenib against placebo. For this reason, we performed a meta-analysis of these two randomized studies and a network meta-analysis (NMA) between sorafenib and lenvatinib, assessing the different outcomes related to the different etiologies.

Materials and methods

Meta-analysis of SHARP trial and Asia-Pacific study

Study design and inclusion criteria

Clinical trials comparing sorafenib and placebo were searched in PubMed. Only randomized controlled trials (sorafenib vs placebo) that included patients with hepatocellular carcinoma were considered eligible and included in the quantitative analysis.

Figure 1 reports the search strategy followed in this meta-analysis. A bibliographic research was conducted of the PubMed, EMBASE, Cochrane Library, and Embase databases. Keyword used included "sorafenib and hepatocellular carcinoma and randomized trial and placebo."

Data extraction and management

Two review authors (ACG and ET) independently screened the titles and abstracts of all the selected studies. All the abstracts of potentially eligible trials were independently read by the same authors that decided if the study was selected. The full text of all selected papers was then analyzed by the same authors to select all the trials finally included in the pooled analysis. When discrepancies in trial search or selection occurred, they were discussed with a third researcher (GLF) to reach a final consensus. The quality of the studies included in this meta-analysis was assessed using the Cochrane risk of bias tool. The risk of bias in this meta-analysis was low.

Statistical analysis

We performed the meta-analysis according to the Prisma statement recommendations.[10] Data were entered in a computer database for transfer and statistical analysis in Review Manager 5.2. Heterogeneity among the trials was assessed with descriptive aim using the I2 test. Any level <5% was considered as statistically significant. HR was the measure of association for time to progression (TTP) and OS. The pooled analysis of HR was performed using a random effect model, fixing a 5% error as index of statistical significance.

NMA of virus etiology

The model for the NMA was fit as previously suggested.[24] Data were extracted from the publications or estimated as proposed by Parmar et al.[25] Treatment effects were estimated by posterior means and 95% credible intervals (CrIs) using random effect, identity link function, and non-informative prior distributions (uniform and normal). We performed 25,000 iterations with burn-in number of 5,000 iterations and a thin interval of 20 to obtain the posterior distributions of model parameters. Convergence was assessed using the Brooks–Gelman–Rubin method. Posterior distributions were used to assess the probability of each treatment to be the best, second best, and so on. Inconsistency and heterogeneity were assessed using node-split models, I2, and Cochran Q tests. Significant heterogeneity was considered to be present for I2>50% or p-value >0.10. Der Simonian and Laird method and random effect were used. All the analyses were made with the R packages "Metaphor" and "Gemtc" (https://www.r-project.org/). The quality of the studies included in this meta-analysis was assessed using the Cochrane risk of bias tool. The risk of bias in this meta-analysis was low.

Results

Meta-analysis of SHARP trial and Asia-Pacific study

Two studies[1,2] were analyzed for this present work. They included 120 and 138 HCC patients treated with sorafenib, and 96 and 87 with placebo for HCV and HBV analysis, respectively. Both studies are sub-analyses of a Phase III trial. The two studies were considered of high quality with low risk of bias.

The results of the meta-analysis showed a significant benefit of sorafenib for HCV-positive patients in terms of TTP (HR 0.39 CI 95% 0.25–0.62 P<0.0001) and OS (HR 0.52 CI 95% 0.36–0.76 P=0.0006) (Figure 1A and Figure 1B). HBV-positive patients showed a trend in favor of sorafenib rather than placebo for TTP (HR 0.74 CI 95% 0.48–1.14 p = 0.18) and OS (HR 0.74 CI 95% 0.544-1.03 p = 0.08) (Figure 1C and Figure 1D). No heterogeneity was detected for the outcomes.

NMA of virus etiology

The NMA was performed on a total of 1,788 patients on six study,[1–26] of these 1160 patients were HCV-positive or HBV-positive. Of these, 251 (21.6%) HBV-positive patients and 91 (7.8%) HCV-positive patients received lenvatinib, whereas 390 (33.6%) HBV-positive patients and 229 (19.7%) HCV-positive patients received sorafenib. A total of 114 (9.8%) HBV-positive patients and 85 (7.3%) HCV-positive patients received placebo. All studies were considered of high quality with low risk of bias.

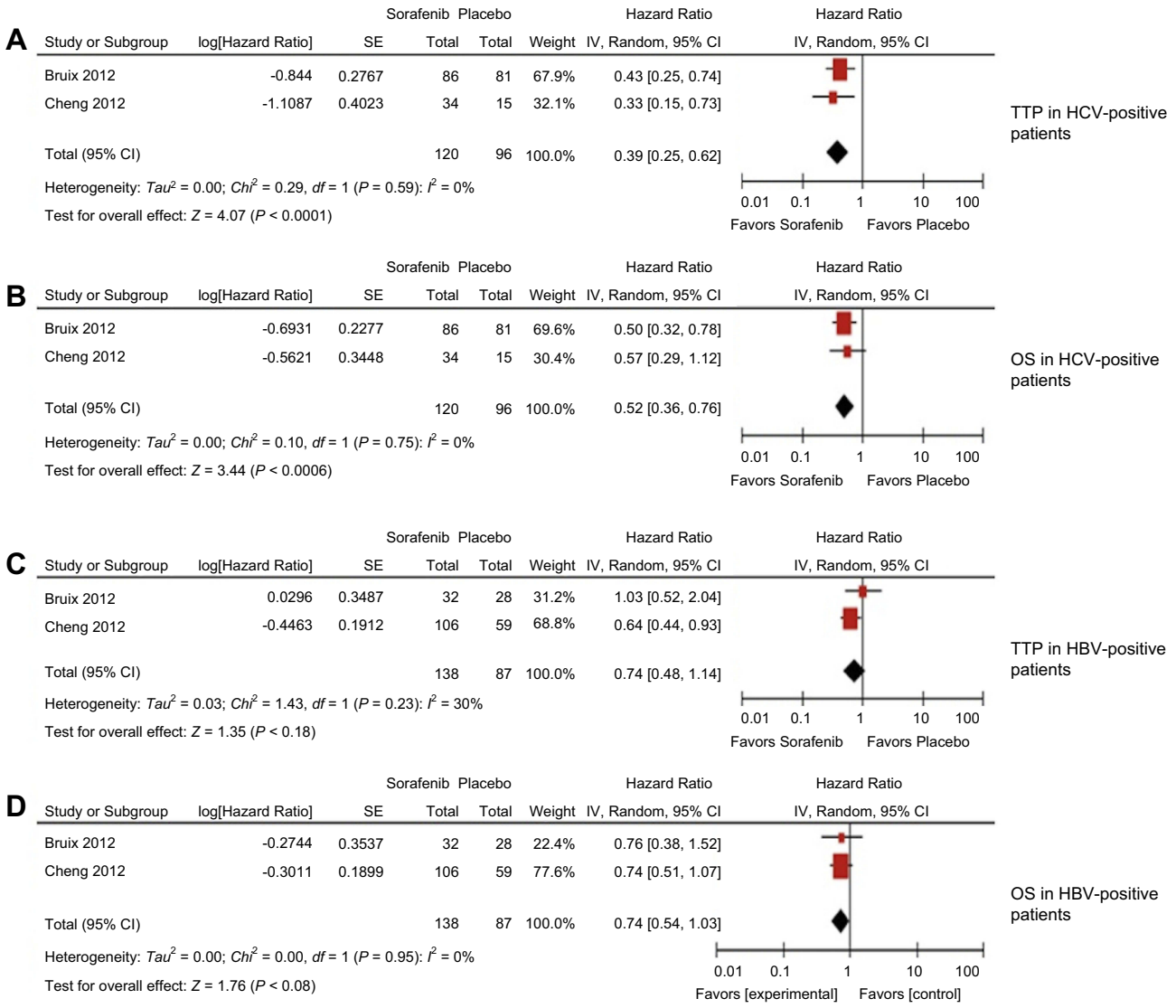

Figure 1 Result of the meta-analysis; time to progression (**A**) and overall survival (**B**) for hepatitis C-positive patients; time to progression (**C**) and overall survival (**D**) for hepatitis B-positive patients.

In the overall population no difference was observed between lenvatinib and sorafenib, despite if a slight trend toward a greater efficacy of lenvatinib (HR 0.92, 95% CrI 0.61–1.36) (Figure 2A). Both lenvatinib and sorafenib were significantly better than placebo.

When we restricted the analysis to HBV-positive patients, a significant benefit in terms of OS was estimated for sorafenib (HR 0.78 95% CrI 0.62–0.97) with respect to placebo; for HBV-positive patients there was a clear trend in favor of lenvatinib over sorafenib (HR 0.82 95% CrI 0.60–1.15) (Figure 2B).

For HCV-positive no differences between lenvatinib and sorafenib were observed (HR 0.91 95% CrI 0.41–2.01) (Figure 2C). I2, Cochran's Q, and node-split models showed no evidence of heterogeneity nor inconsistency, strengthening the results of the NMA.

The rankogram in Figure 3 reports the probably best approach for these patients. The rankogram shows that Lenvatinib was probably the best approach for HBV-positive patients.

Discussion

Lenvatinib has a biological rationale for use in patients with advanced HCC. The REFLECT study was well designed, despite being open-label.[6]

What is key to our study is whether a non-inferiority study can change clinical practice. Table 1 lists the most important factors that may influence this choice of

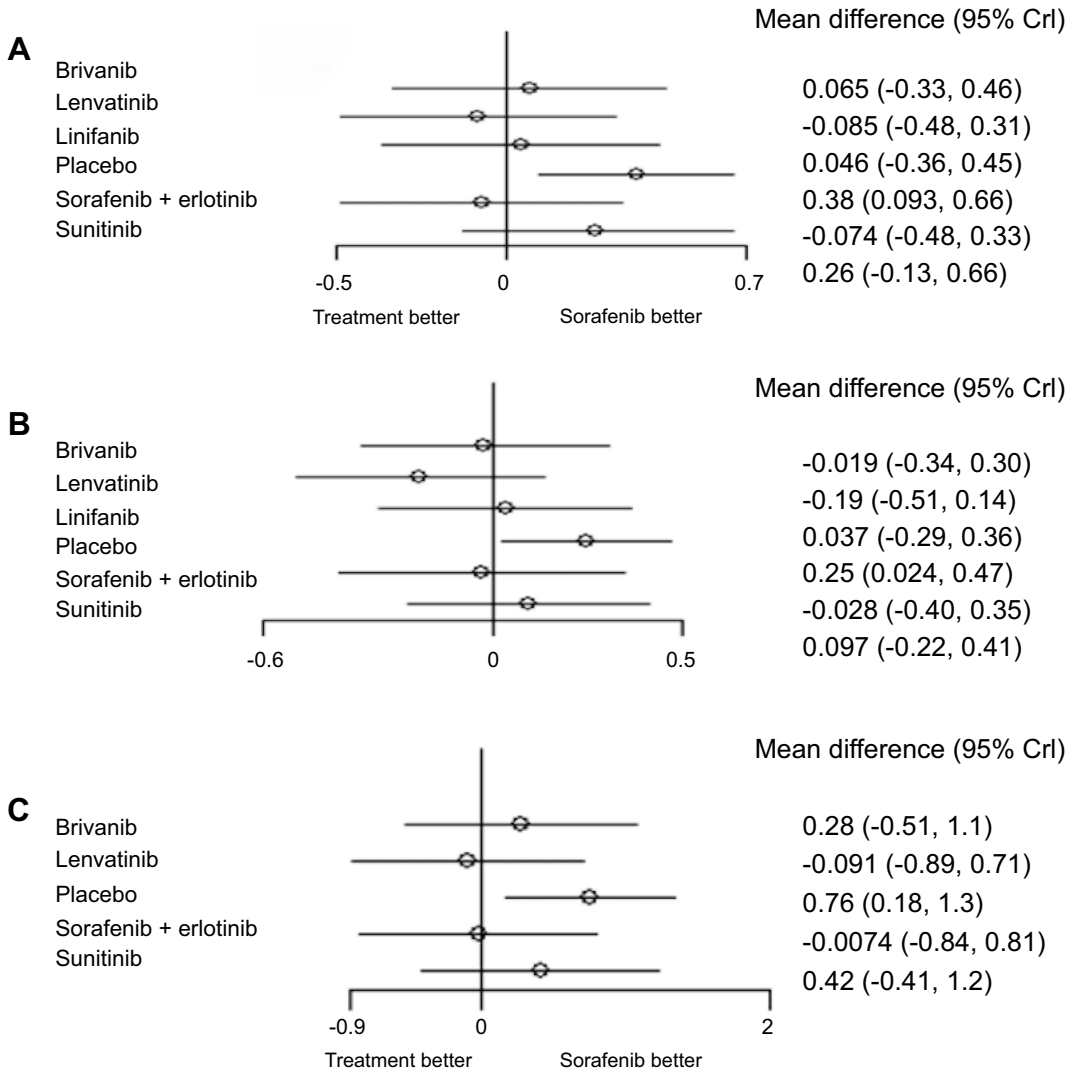

Figure 2 Results of Network Meta Analysis in all population **(A)**; hepatitis B-positive patients **(B)** and hepatitis C-positive patients **(C)**.

treatment. The first is the toxicity profile compared to the standard of care. Lenvatinib showed a non-negligible safety profile, proving no advantage against sorafenib: patients in the sorafenib arm had more dermatological AEs, but less hypertension than patients in the lenvatinib arm. Generally, dermatological AEs carry no risk of death, although they often compromise the patient's quality of life (QoL), and can be resolved by dose decrease or treatment interruption. Patients receiving lenvatinib had a better QoL, as also demonstrated by a sub-analysis of the REFLECT study. However, hypertension can be rarely associated with serious complications regardless of treatment interruption. The second factor is the cost of the new drug compared to the standard of care: a lower price with similar efficacy and toxicity profile can well influence the doctor's decision in clinical practice. Finally, patients who tolerate sorafenib may undergo regorafenib for disease progression as an effective second-line alternative, whereas no results are available about any effective option for disease progression beyond lenvatinib.

In the context, the identification of biomarkers or clinical parameters that could predict response or resistance to treatments is needed to guide treatment decision.

Our data from NMA highlighted that lenvatinib has a greater activity in HBV-positive patients. The data showed that lenvatinib could be the best drug for HBV-positive patients in 59% of cases compared to only 1% of patients treated with sorafenib.

This is a crucial point because actually we could have clinical parameters to select better the best treatment for

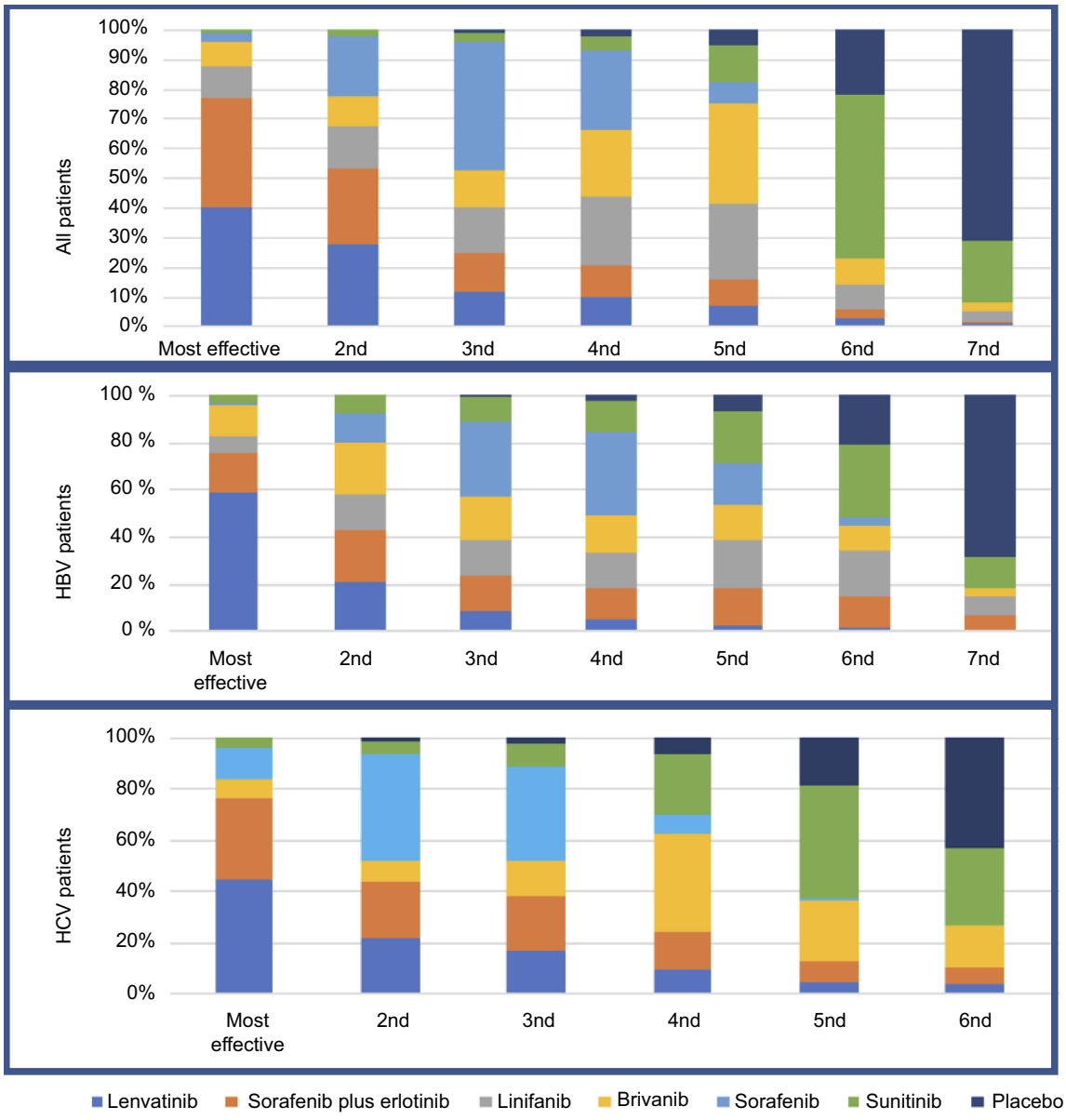

Figure 3 Rankogram of theNetwork Meta analysis.

the patients. Our findings seem to confirm previous suggestions on this topic although further confirmatory data may be necessary.

We believe that future prospective studies should aim to customize therapy based on the etiology. For example, a sub-analysis of the RESOURCE study[27] highlights, as we have already pointed out,[28] that the HR for OS was 0.58 (95% CI 0.41–0.82 *P*=0.0009) in HBV-positive patients against 0.79 (95% CI 0.49-1.26 *P*=0.1583) in HCV-positive patients. Similar data were observed for PFS (0.39 vs 0.59, respectively) and TTP (0.38 vs 0.57, respectively). Actually, we have more drug in advanced hepatocellular in the same line. Future study must be aimed to identify a best strategy in first and second line.

Conclusion

In conclusion, the identification of clinical or biological markers that could predict response or resistance to treatments is needed to guide treatment decision. This NMA demonstrates that the etiology is a good candidate and this result should be validated in a specific trial.

Table 1 The main results of the REFLECT trial

	LENVATINIB	SORAFENIB	In favor of:
Overall survival (months, 95% CI)	13.6 (12.1–14.9)	12.3 (10.4–13.9)	EQUAL
Time to progression (months, 95% CI)	8.9 (7.4–9.2)	3.7 (3.6–5.4)	LENVATINIB
Disease control rate (%, 95% CI)	36.1 (75.5%, 71.7–79.4)	28.8 (60.5%, 56.1–64.9)	EQUAL
Total treatment-emergent adverse events (%)	99%	99%	EQUAL
Treatment-related, treatment-emergent adverse events of grade ≥3 (%)	57%	49%	EQUAL
Serious treatment-emergent adverse events (%)	43%	30%	SORAFENIB
Palmar-plantar erythrodysesthesia grade ≥3 (%)	3%	11%	LENVATINIB
Hypertension grade ≥3 (%)	23%	14%	SORAFENIB
Option beyond didease progression	NO	YES	SORAFENIB
Cost	Unknown	Unknown	Unknown
Quality of life	Unknown	Unknown	LENVATINIB

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Author contributions

All authors contributed to data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspectes of the work.

Disclosure

ACG is on the advisory board for Eisai Co., Ltd. SC received personal fees from Bayer and grants from Eisai Co., Ltd, personal fees from Lilly and personal fees from Servier. MS received grants and personal fees from Merck, grants and personal fees from Bayer, personal fees from Eisai Co., Ltd., personal fees from Bristol-Myers Squibb, grants from Merck and personal fees from AMGEN. The authors report no other conflicts of ineterest in this work.

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