Efficacy and Safety of Systemic Therapies for Advanced Hepatocellular Carcinoma: A Network Meta-Analysis of Phase III Trials

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Abstract
Aim/Background: After the introduction of sorafenib in the treatment of advanced hepatocellular carcinoma (HCC), different studies tried to evaluate whether other systemic therapies can improve survival. To provide a comprehensive indirect treatment comparison of efficacy and safety of novel drugs, a network meta-analysis (NMA) of phase III randomized controlled trials was performed. Methods: After pertinent literature search up to November 1, 2016, 6 studies were eligible for the analysis including 4,812 individual patients with advanced HCC: 2,454 received sorafenib, 577 received brivanib, 530 received sunitinib, 514 received linifanib, 358 received sorafenib + erlotinib and 379 received placebo. Frequentist NMA was used to compare treatments within a single analytical framework. Results: NMA showed that sorafenib alone, regardless of combination with erlotinib, and linifanib provide a significant survival advantage over placebo (p < 0.05) but without any significant difference between each other. Conversely, all regimens significantly ameliorate progression-free survival versus placebo (p < 0.05). The rank order of efficacy was: sorafenib ± erlotinib, linifanib, brivanib, sunitinib, and placebo. Sorafenib ± erlotinib was the regimen with the fewest number of adverse events that required discontinuation of treatment, whereas linifanib and brivanib resulted in the most adverse events. The risk-benefit summary identified one cluster of therapies with a similar
balance between efficacy and safety which included sorafenib alone or in combination with erlotinib, having, at the same time, the highest efficacy and safety. **Conclusions:** Sorafenib remains the best systemic treatment for advanced HCC; linifanib also resulted in survival advantages over placebo but with a lower safety profile.

**Introduction**

Sorafenib is an oral multikinase inhibitor with effective antiangiogenic and proapoptotic activity and marked antitumoral effect in patients with hepatocellular carcinoma (HCC) [1, 2]. The improvement of survival in the patients treated with sorafenib is supported by the evidence derived from 2 phase III randomized controlled trials (RCTs) [3, 4]. According to the European Association for the Study of Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines, sorafenib is currently considered the standard systemic therapy for patients with advanced stage HCC and well-preserved liver function [5, 6]. Based on the increasing knowledge of the large number of molecular pathways involved in HCC growth, numerous target-specific and/or broad-spectrum tyrosine kinase inhibitors (TKIs) have been developed and tested in different phase II and III trials in HCC [7]. These trials came after the licensing of sorafenib in 2007 attempting to test if further improvement in patient survival, with better safety profile, is possible.

In presence of new antitumoral agents, it would be useful to summarize and rank efficacy and safety of such different treatments. This is particularly important when more agents are approved for the same indication (e.g., first-line treatment), but not all direct comparisons have been carried out. Even though only one agent is approved for first-line therapy for HCC at present, a comparison of efficacy and safety of the different molecules tested so far, among each other, could also be relevant to highlight the roles and the importance of different mechanisms of action in this particular clinical setting. In fact, the various agents tested in first line, have different antiangiogenic and antiproliferative potential and target receptors, although they nearly all belong to the TKI class. To produce such a comparison of multiple different agents each with another, a multiarm trial would be necessary, but unfortunately it is unlikely that such level of evidence will ever become available, and to our knowledge there are no plans to conduct such a trial [8, 9]. This lack of direct comparison can be analytically compensated by adopting a multiple (mixed) treatment indirect comparison through development of a network meta-analysis (NMA) [8, 9]. NMA is a technique to meta-analyze networks of trials comparing two or more treatments at the same time. It has advantages over conventional pairwise meta-analysis, as this technique borrows strength from indirect evidence to gain certainty about all treatment comparisons, allowing estimations of comparative effects that have not been investigated in the head-to-head RCTs. Using hierarchical model, all direct and indirect comparisons are taken into account to attain at a single consistent estimate of the effect of all included treatments based on all included studies.

The aim of this study was thus to perform an NMA that takes into account efficacy and safety of different systemic therapies in the treatment of advanced HCC, as defined by the EASL/AASLD guidelines, which were tested in phase III RCTs. Such treatment network of available highest quality studies can offer the exceptional opportunity to compare the evidence available for each treatment with all others in the setting of advanced HCC.
Methods

Literature Search Strategy

A systematic search of PubMed, ISI Web of Knowledge and Cochrane Central Register of Controlled Trials (CENTRAL) databases was performed for articles published until 1 November 2016 relevant to the use of sorafenib and different pharmacotherapies in the systemic treatment of advanced HCC. PubMed database was searched using the following key words: "sorafenib" [Supplementary Concept] OR "sorafenib" [All Fields] AND "(carcinoma, hepatocellular" [MeSH Terms] OR "hepatocellular carcinoma") with the flag "randomized controlled trial" on. ISI Web of Knowledge was searched using the following terms: TS = "hepatocellular carcinoma" AND "sorafenib" AND (TS = randomized controlled trial). CENTRAL database was searched using the following key words: "hepatocellular carcinoma".ti,ab,kw and "sorafenib" and "randomized controlled trial":pt (Word variations have been searched). The search was limited to human subjects and focused on RCTs. No language limitations were imposed. Additional articles were searched in the International Clinical Trials Registry Platform (ICTRP) and Google Scholar without retrieving any additional available study. The reference list of identified RCTs was also manually searched until no additional eligible trials could be identified. Results from the three electronic databases were compared to obtain a single list of individual articles for screening.

Literature Screening

One author (A.C.) conducted the initial screening of the generated single list of individual articles to identify all relevant studies meeting our eligibility criteria (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000481314). Reviews, letters to the editors, study protocols, and congress abstracts were excluded at this step. Then, 2 independent reviewers (F.P. and F.M.) assessed the studies for relevance, inclusion, and methodological quality. Inclusion criteria were the following: (1) phase III RCT as study design; (2) study intervention in which the treatment arm received Sorafenib-only therapy and the control arms received other pharmacotherapies or sorafenib-based therapies or placebo as first-line treatment; (3) study population consisted of adult patients with advanced HCC with an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less; adequate hepatic, hematological, and renal function as defined in each of retrieved studies and a life expectancy of 12 weeks or more; (4) primary outcome measure was overall survival, and the secondary outcomes included progression-free survival (PFS) and adverse events (AEs). For the last level of screening, the full text was obtained for relevant articles as well as for any citations for which a decision could not be made on the basis of the abstract. In case the same trial appeared in different publications, only the most informative article was retained to avoid duplicate information. Such linked studies were identified on the grounds of authorship, institutions, design, length of follow-up, and study populations. If additional data or results were needed, the corresponding author of each report was contacted by e-mail. Any discrepancies in inclusion were resolved by discussion between the reviewers and a third investigator (A.C.).

Data Collection and Statistical Analysis

Data derived from retrieved/included studies were collected in an Excel file. Two investigators (F.P. and F.M.) extracted in a piloted form the following data from each study: first author, year of publication, number of patients for each treatment arm, performance status, number of patients with macroscopic tumour vascular invasion, number of patients having extrahepatic disease, overall survival, time to progression, and AEs. The main outcome measures were patient survival (efficacy) and discontinuation due to drug-related AEs (safety) whereas PFS was considered as secondary outcome measure. Numbers of events, at-risk patients, and censored patients for survival and time-to-progression were estimated from Kaplan-Meier survival curves in the interval of 0–12 months, using the appropriate formulas proposed by Tierney et al. [10]. The total person-time at risk and the mortality or the progression × 100 person-months were properly estimated [10]. Since studies were all RCTs, the methodological quality of each study was assessed using the RoB 2.0 tool [11]. The principal summary measure was hazard ratio (HR) for time-dependent efficacy events and risk ratio for safety events.

Frequentist NMA was used to compare available treatment strategies within a single analytical framework [12]. NMA was performed with Stata 14.0 (StataCorp., College Station, TX, USA) using the “network” command and routines developed by Chaimani and White [12, 13]. The relative ranking probability of each treatment was estimated, and rankograms were used to estimate the hierarchy of each intervention in terms of both efficacy (patient survival and PFS) and safety (discontinuation due to AEs). The mean
Table 1. Main characteristics of the phase III trials retrieved and included in the network meta-analysis

| First author, year [Ref.] | Treatment | n     | Age, years | HCV, % | ECOG-0, % | MaVI, % | EHD, % | Mortality, ×100 person-months | Progression, ×100 person-months | Discontinuation, % |
|---------------------------|-----------|-------|------------|--------|-----------|--------|-------|-------------------------------|-------------------------------|-------------------|
| Llovet, 2008 [3]          | sorafenib | 299   | 64.9 ± 11.2 | 29.1   | 53.8      | 36.1   | 53.2  | 7.7                           | 15.0                          | 11.4              |
|                           | placebo   | 303   | 66.3 ± 10.2 | 27.1   | 54.1      | 40.6   | 49.5  | 9.5                           | 27.2                          | 5.0               |
| Cheng, 2009 [4]           | sorafenib | 150   | 52.8 ± 18.2 | 10.7   | 25.3      | 36.0   | 68.7  | 11.8                          | 27.8                          | 19.5              |
|                           | placebo   | 76    | 52.0 ± 15.6 | 3.9    | 27.6      | 34.2   | 68.4  | 17.3                          | 40.6                          | 13.3              |
| Johnson, 2013 [14]        | sorafenib | 578   | 58.5 ± 18.5 | 20.6   | 60.9      | 27.3   | 50.3  | 14.1                          | 22.0                          | 14.8              |
|                           | brivanib  | 577   | 57.0 ± 19.6 | 20.1   | 62.6      | 26.9   | 49.0  | 14.5                          | 22.4                          | 20.9              |
| Cheng, 2013 [15]          | sorafenib | 544   | 55.0 ± 19.0 | 21.9   | 52.9      | 37.9   | 38.4  | 13.8                          | 24.6                          | 12.7              |
|                           | sunitinib | 530   | 55.3 ± 19.3 | 21.3   | 52.5      | 42.6   | 36.2  | 15.3                          | 26.2                          | 13.3              |
| Cainap, 2015 [16]         | sorafenib | 521   | 57.5 ± 18.5 | 24.8   | 66.0      | 40.5   | 56.8  | 12.7                          | 21.1                          | 25.4              |
|                           | linifanib | 514   | 55.8 ± 18.2 | 25.3   | 62.8      | 46.3   | 59.7  | 12.8                          | 21.6                          | 36.3              |
| Zhu, 2015 [17]            | sorafenib (+ placebo) | 362   | NA         | 23.2   | 59.7      | 42.3   | 60.5  | 15.6                          | 18.0                          | 34.6              |
|                           | sorafenib + erlotinib | 358   | NA         | 29.9   | 62.0      | 38.5   | 57.3  | 14.5                          | 18.1                          | 32.3              |

Values for age are expressed as mean ± standard deviation. HCV, hepatitis C virus (positivity); ECOG, Eastern Cooperative Oncology Group; MaVI, macroscopic vascular invasion; EHD, extrahepatic disease; NA, not available or not assessable. a Calculated from median and range using the formula proposed by Hozo et al. [18]; the paper from Zhu did not report ranges to estimate the mean and the SD of patient age. b Indirectly estimated from baseline features reported in the paper. Heterogeneity values of τ for age = 4.943, HCV = 0.226 (after the exclusion of Cheng's work τ = 0.147), ECOG-0 = 0.333, MaVI = 0.268, EHD = 0.361.
rank values and the surface under the cumulative ranking (SUCRA) curves were also calculated [9, 12, 13]. SUCRA is a relative ranking measure that derives from using the rank probabilities from rankograms (the cumulative rank curves) and that accounts for the uncertainty in treatment order, that is, accounts both for the location and the variance of all relative treatment effects. In analogy to the area under a receiver operating characteristic curve, the SUCRA value can range from a minimum of 0 (worst) to a maximum of 1 (best). Thus, the larger the SUCRA value, the better the rank for a specific treatment among the n available treatment options. As supplementary information, clustered ranking plot was constructed using SUCRA values for efficacy (overall survival) and safety (discontinuation due to AE) outcomes to obtain information on meaningful groups of treatments that maximize benefits [13]. The network was also checked for inconsistency to assess when the direct comparison of one treatment versus another one, derived from one or more studies included in the NMA, conflicts with evidence drawn via the indirect comparison estimated through the NMA; however, few direct comparisons were present to formally detect inconsistency in the present model [9, 12, 13]. The restricted maximum likelihood method was used to estimate heterogeneity, assuming a common variance estimate across different comparisons for each single outcome considered [12]. The extent of heterogeneity in each network analysis was evaluated and measured through a common heterogeneity variance for the network (τ) considering the range of expected treatment estimates (HRs and risk ratios). Values of τ between 0.1 and 0.5 were considered reasonable, between 0.5 and 1.0 were considered fairly high, and larger than 1.0 represented extreme heterogeneity. The NMA was reported in accordance with the modified PRISMA guidelines for network meta-analyses [9].

Results

Literature Search Results

A total of 89 unique articles were identified using our search criteria for screening (see online suppl. Fig. 1). Following assessment by the adopted exclusion criteria, 83 articles were excluded and 6 phase III RCTs were retained for NMA (Table 1) [3, 4, 14–17]. The complete list of excluded studies and the causes of exclusion are reported in the online supplementary Table 1. The risk of bias according to the RoB 2.0 tool was graded as “low” for most of domains (see online suppl. Fig. 2). The NMA was developed on a total of 4,812 individual patients with HCC fulfilling eligibility criteria. Of these, 2,454 received sorafenib (51.0%), 577 received brivanib (12.0%), 530 received sunitinib (11.0%), 514 received linifanib (10.7%), 358 received sorafenib in combination with erlotinib (7.4%) and 379 received placebo (7.9%). The structure of the NMA is reported in Figure 1, and further details of the included literature are provided in the online supplementary Table 2.

NMA of Efficacy

Efficacy from NMA was first investigated having placebo as comparator (Fig. 2). As expected, a significant benefit in terms of overall survival was estimated for sorafenib (HR = 0.69; 95% CI: 0.58–0.84); however, a benefit was also indirectly estimated for the adoption of sorafenib + erlotinib (HR = 0.67; 95% CI: 0.51–0.88) and for linifanib therapy (HR = 0.73; 95% CI: 0.57–0.93) over placebo. On the contrary, the indirect estimate of overall survival benefit for brivanib and for sunitinib against placebo was found not statistically significant (95% CI of the HR included the value of 1). When instead assessing the PFS, all the regimens tested were found to be significantly associated with a longer PFS than placebo; the heterogeneity for both overall survival and PFS was deemed to be low (τ <0.1) and no inconsistency was observed (Fig. 2).

NMA results for each possible combination between different pharmacotherapies are reported in Table 2. This “league table” reports, in terms of HR of overall survival and PFS, the relative benefit (if any) obtainable from one therapy against all the other considered. In terms of overall survival, Sorafenib alone or in combination with erlotinib was found superior to sunitinib (HR = 0.80; 95% CI: 0.69–0.94 and HR = 0.77; 95% CI: 0.60–0.99), whereas no differ-
Fig. 1. Diagram showing the NMA structure and the information provided. Continuous lines indicate head-to-head direct comparison of 2 drugs obtained from RCTs (first author of each trial reported in the corresponding box with year of publication). Dashed lines indicate indirect treatment comparisons, whose outcome measures are extrapolated from the meta-analysis of other direct comparisons in RCTs. Circles at the knots of the network indicate treatment molecules, with the size of the circle being approximately proportional to the total number of enrolled patients.

Fig. 2. Hazard ratio (HR) for overall survival (upper bars in each row with diamond-shaped marker) and for progression free survival (square-shaped marker) of each therapy when compared to placebo. Note that head-to-head RCT versus placebo was directly performed only for sorafenib, whereas information about all other drugs could only be provided through the NMA of the present study. The τ values for overall survival and PFS were <0.1 for both, indicating low heterogeneity.
ences in comparison with linifanib or brivanib were observed. Furthermore, the addition of erlotinib to sorafenib did not result in any gain in patient survival in comparison to sorafenib alone. In terms of PFS, sorafenib either alone or in combination with erlotinib, and linifanib were found superior to sunitinib (HR = 0.81; 95% CI: 0.65–0.99; 95% CI: 0.71–0.91 and = 0.80; 95% CI: 0.67–0.97, respectively). Again, the addition of erlotinib to sorafenib did not modify the PFS (Table 2).

The probabilities of being the best treatment in terms of overall survival are reported in the rankogram of Figure 3a. The combination of erlotinib with sorafenib was the most probable best approach considering overall survival, ranking first in 58.5% of hypothetical cases, whereas sorafenib was estimated to be the best approach in 21.3% of hypothetical cases. Either one or the other therapeutic regimen fitted as the first or the second best treatment in about 75% of hypothetical cases. The mean rank values for survival, among the 6 possible therapies, were as follows: sorafenib + erlotinib = 1.8 (SUCRA = 0.847), sorafenib alone = 2.1 (SUCRA = 0.788), linifanib = 2.8 (SUCRA = 0.636), brivanib = 3.7 (SUCRA = 0.469), sunitinib = 4.9 (SUCRA = 0.225), placebo = 5.8 (SUCRA = 0.036).

**NMA of Safety**

The rankogram of Figure 3b reports results from NMA when considering discontinuation due to drug-related AEs. The safest treatment is the one showing the lowest incidence of discontinuation and was obviously estimated for placebo. Sorafenib without or with the addition of erlotinib showed a very good safety profile, being the first two most tolerated active drugs. On the contrary, brivanib and linifanib were the therapies most frequently associated with discontinuation of treatment due to AEs. The mean safety rank values, among the 6 possible therapies, were as follows: placebo = 1.0 (SUCRA = 0.995, least associated with

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**Table 2.** League table presenting network meta-analysis estimates of efficacy (hazard ratio) for patient survival and progression-free survival of different pharmacotherapies in the treatment of advanced hepatocellular carcinoma

| Treatment            | Patient survival | Progression-free survival |
|----------------------|------------------|---------------------------|
| Sorafenib + ERL      | 0.96 (0.79–1.17) | 1.00 (0.85–1.19)          |
| Sorafenib            | 0.92 (0.72–1.19) | 1.00 (0.87–1.15)          |
| Linifanib            | 0.90 (0.77–1.05) | 0.89 (0.72–1.11)          |
| Brivanib             | 0.94 (0.75–1.17) | 0.89 (0.72–1.11)          |
| Sunitinib            | 0.87 (0.68–1.11) | 0.87 (0.68–1.11)          |
| Placebo              |                  |                           |

**Note:** Treatments are reported in order of relative ranking for efficacy. Comparisons between treatments should be read from left to right, and their hazard ratio is in the cell in common between the column-defining treatment and the row-defining treatment (as an illustrative example, considering patient survival, if one is interested to compare sorafenib + erlotinib with sunitinib, the hazard ratio would be of 0.77 [95% CI 0.60–0.99]). Hazard ratios of direct comparison trials calculated from NMA are equal to those of trials involved, confirming the goodness-of-fit of the present NMA. Hazard ratio < 1 means the treatment in top-left is better; values reported in bold have *p* values < 0.05. ERL, erlotinib.
Fig. 3. Rankogram reporting the probabilities of being the best treatment (reflective of the length in stacked bar for each drug in given column) in terms of overall survival (a) or of highest safety (b). For instance, sorafenib-based therapies have 80% probability of being the most effective treatments in terms of overall survival (either sorafenib as a single agent [21.3%], or in combination with erlotinib [58.5%]). At the same time sorafenib-based therapies were associated with a probability of around 80% of being the 2nd or the 3rd safest therapy (placebo being the 1st) due to discontinuation of treatment secondary to adverse events (AEs). The τ value for safety was 0.05, indicating low heterogeneity within the NMA.

Fig. 4. Graph displaying the surface under the cumulative ranking values (SUCRA) for efficacy (x axis) together with the values for safety (discontinuation due to drug-related adverse events, y axis). A cluster of treatments was identified having similar and best risk-benefit balance, which included sorafenib ± erlotinib. Higher SUCRA values are associated with higher efficacy and higher safety (highest for both axis = 1).
discontinuation due to AEs), sorafenib + erlotinib = 2.6 (SUCRA = 0.685), sorafenib alone = 3.1 (SUCRA = 0.579), sunitinib = 3.5 (SUCRA = 0.509), brivanib = 5.4 (SUCRA = 0.126) and linifanib = 5.5 (SUCRA = 0.105). The heterogeneity for safety was deemed to be low (τ <0.1) and, again, no inconsistency was observed.

Detailed mean rank and SUCRA values for grade 3–4 diarrhea, hand-foot syndrome, hypertension, vomiting, and liver dysfunction are reported in the online supplementary Table 3. Finally, by plotting SUCRA values for efficacy (overall survival) concurrently with the values for safety (discontinuation), a cluster of treatments was identified having similar risk-benefit balance, which included sorafenib ± erlotinib with the highest efficacy and safety being present at the same time (Fig. 4).

**Discussion**

The present NMA compared all drugs and placebo that have been tested in first-line phase III RCTs up to end of 2016. Through the present analytical methodology, it was possible to produce new original information, which confirmed sorafenib as the most efficacious molecule, and claiming it as the only one licensed drug for HCC in Western countries. No other drugs can be recommended to be used in off-label setting, and sorafenib should remain the mainstay of systemic treatment for advanced HCC.

After the pivotal registration trials that showed a prolongation of survival under sorafenib in comparison to placebo [2, 3] and before the current study, a number of drugs have been tested against sorafenib [19]. None of these alternative drugs produced an overall survival benefit meeting the criteria for the Food and Drug Administration for approval (namely, that the upper value of the 95% CI of the hazard ratio does not exceed 1.08) [20]. At the same time, it is not clear if these drugs would have been better than placebo, if directly tested. The present study showed that a hypothetical direct comparison with placebo would likely have not produced a significant superiority for brivanib and sunitinib (HR spanning over the unit value; Table 2; Fig. 2), although all compounds produced improvement in the PFS compared to placebo (Table 2; Fig. 2). Our NMA also allowed to confirm in a very large number of subjects (more than 2,000 individuals treated with sorafenib much larger than those included in the registration trials) that sorafenib-based therapies are not only better than placebo but that are associated with the higher efficacy than any other tested molecule (Table 2). The combination of sorafenib with erlotinib produced minimally and negligible better efficacy to sorafenib alone, at the expenses of greater toxicity and costs. Reasons for failure of new drugs to be superior, or at least noninferior, to sorafenib were hypothesized to be various, including the lack of understanding of critical drivers of tumor progression/dissemination, liver toxicity, flaws in trial design, or marginal antitumoral potency [20]. The present analysis provided a comprehensive overview of efficacy and safety of all drugs tested in RCTs so far.

The current results can be viewed in the light of the current knowledge of mechanisms of actions of drugs compared in this NMA. In fact, although all the tested drugs are TKI and almost all of them include an antiangiogenic effect, they all have slightly different targets and different modalities of action (suppl. Table 4), and even when acting on the same final target they possess different potencies in vitro. In the setting of HCC, that is most often superimposed on a background of liver cirrhosis, involving a severe intra-hepatic and splanchnic vascular and angiogenic derangements, maximal potency (either due to the mechanism of action or drug dosage) does not always translate into maximal efficacy due to the potential risk of AEs [20, 21]. For instance, sunitinib was claimed to be a more potent antiangiogenic compound than sorafenib based on the zebrafish model (see online suppl. Table 4) [22], but does not target as efficiently the antiproliferative pathway as sorafenib and, differently from
the expectations, the final clinical effect at the tested dosage was a more toxic drug than sorafenib, with a trend to poorer, rather than better survival (Fig. 3) [15].

The potential of some drugs, such as brivanib or sunitinib, to inhibit fibroblast growth factor (FGF) concurrently with vascular endothelial growth factor (VEGF) raised high hopes that the inhibition of FGF could maintain the antiangiogenic effect in tumor clones that had become resistant to VEGF inhibition, thereby improving the length of tumor response [23]. Unfortunately, the assessment of clinical effects did not confirm the hypothesis derived from cellular data [14, 15]. Probably, it is not just a matter of the affected tumor pathways, but also of the potency of the molecule to achieve one or another action and of the effect of the drug on background liver function, portal hypertension as well as on other organs, which are hard to predict from laboratory data. Unfortunately, an established and reliable model of HCC in the setting of liver cirrhosis still does not exist in the preclinical animal setting, stressing the need for well-performed and large enough phase II trials, at best with a randomized design [24]. In the absence of the possibility to accurately predict in vivo results from in vitro findings, the only way to test the effect of promising molecules are clinical trials. Thus, the results of the current meta-analysis could provide insights about the role of potential pathways, to speculate if a new future molecule could be associated with a theoretical higher or lower likelihood of clinical effectiveness, hence deserving or not to be tested in future clinical trials.

The present study is subject to limitations inherent to all NMAs in terms of both quality of the included studies, heterogeneity of studied populations, and transitivity assumption. Defects in the design, management, and analysis of RCTs can lead to bias, raising concerns about the strength of the included findings. The trials included in the present NMA were, however, all phase III trials, with similar inclusion criteria and low risk of bias for most of domains analyzed (RoB 2.0, see online suppl. Fig. 2). Despite similar inclusion criteria, a nonnegligible heterogeneity can be perceived from observing clinical baseline characteristics of the 6 different RCTs (Table 1). This may question the NMA assumption of transitivity. However, the τ values from NMA of efficacy and safety grossly remained below the threshold value of 0.1 (Table 2; Fig. 3) which provides additional assurance about validity of our analysis. In addition, due to the "star-structure" of the present NMA, it was not possible to get any inconsistency (that is when the direct comparisons conflict with evidence drawn via the indirect comparisons estimated through the NMA), and this feature represent a further strength of the present study [9]. All these aspects confirm the goodness of the present model but also advocate that present results should be considered in light of these uncertainties intrinsic to the methodology of the NMA.

A particular mention should be made of the role of hepatitis status in determining response to sorafenib therapy. It has recently been shown that the impact of sorafenib is largely confined to the patients who are HCV positive [25, 26]. The present NMA cannot account for this specific aspect to be ascertained, and the investigation of this issue would require subgroup efficacy and safety data segregated for HCV positive and negative patients. However, by analyzing the specific percentages of HCV-positive patients in each of the trial involved, we observed no statistical difference between HCV prevalence in the sorafenib group and in the comparator group (relative risk: 0.98; 95% CI: 0.86–1.11). On one side, this can reassure for the transitivity of the NMA with regard to HCV status, but on the other side we need to point out that the viral status should be considered when developing further meta-analytic approaches, such as the present NMA, with the possible access to completed trial data [27].

A final mention should be made of the new ongoing trials. In particular, the phase III REFLECT trial, involving 954 patients with unresectable HCC (January 25, 2017), achieved the primary end-point (overall survival) in the lenvatinib group, not inferior to that with sorafenib and with a longer, statistically superior, PFS [27, 28]. At the time the present NMA
was developed, results from the REFLECT trial were still not published, but considering the primary end-point (overall survival) it would be unlikely that lenvatinib inclusion would change present results (Fig. 4). However, it would be of interest to rank this drug in terms of PFS against placebo and the other antiangiogenic therapies included in the current NMA. Thus, further high-level evidence is keenly awaited.

In conclusion, the results of the present NMA support the use of sorafenib as the mainstay systemic treatment for advanced HCC. All other molecular compounds can improve PFS but only linifanib demonstrated improvement in the overall survival in these patients. The balance between efficacy and safety favors sorafenib as the optimal choice for management of HCC. Our analysis can be useful in development of new molecules for treatment of HCC.

**Disclosure Statement**

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**Author Contributions**

A. Cucchetti and F. Mazzotti had the original idea and planned the study; F. Piscaglia and F. Mazzotti performed the literature review; A. Cucchetti and B. Djulbegovic performed the network meta-analysis; F. Piscaglia and A. Cucchetti interpreted the results and wrote the manuscript; A.D. Pinna and L. Bolondi provided expertise for important intellectual content of the manuscript.

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