BMJ Open

The optimum systemic treatments for advanced/metastatic renal cell carcinoma of favorable-, intermediate-, and poor-risk, respectively: a Bayesian network analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034626
Article Type:	Original research
Date Submitted by the Author:	06-Oct-2019
Complete List of Authors:	Cao, Guanghui; Henan Provincial People's Hospital Wu, Xiaoqiang; Henan Provincial People's Hospital Wang, Junpeng; Henan Provincial People's Hospital Wang, Zhiwei; Henan Provincial People's Hospital Wu, Xuan; Henan Provincial People's Hospital Zhang, Haotian; Henan Provincial People's Hospital Jing, Gaopeng; Henan Provincial People's Hospital Yan, Tianzhong; Henan Provincial People's Hospital,
Keywords:	Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY, IMMUNOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The optimum systemic treatments for advanced/metastatic renal cell carcinoma of favorable-, intermediate-, and poor-risk, respectively: a Bayesian network analysis

Guanghui Cao, Xiaoqiang Wu, Junpeng Wang, Zhiwei Wang, Xuan Wu, Haotian Zhang, Gaopeng Jing, Tianzhong Yan

Department of Urology, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Zhengzhou 450003, China;

[#] Correspondence to Prof Tianzhong Yan PhD, Department of Urology, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Zhengzhou 450003, China.

E-mail address: ytz460@hotmail.com (Tianzhong Yan), wuxiaoqiang2005@126.com (Xiaoqiang Wu).

Tel.: + 86 731 87160355; fax: + 86 431 87160356.

Abstract

Purpose: Advanced/metastatic renal cell carcinoma (RCC) is a heterogeneous group of conditions with different risk stratification. The optimum systemic therapies for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk have not been established. We aimed to compare and rank the effects associated with systemic therapies in the first-line setting.

Methods: We searched Pubmed, Cochrane databases, Web of Science, and ClinicalTrials.gov for randomized controlled trials (RCTs) published up to September 2019, of the above 11 treatments for advanced/metastatic RCC. Analysis was done on a Bayesian framework.

Results: 13 unique RCTs including 7 248 patients were identified. For advanced/metastatic RCC of favorable-risk, temsirolimus plus bevacizumab, and nivolumab plus ipilimumab were associated with significantly worse progression-free survival (PFS) than sunitinib (HR 1.96, 95% CI 1.04-3.63; and HR 1.56, 95% CI 1.32-1.84, respectively). For intermediate-risk patients, nivolumab plus ipilimumab and cabozantinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.66, 95% CI 0.54-0.81; HR 0.64, 95% CI 0.43-0.96, respectively). For poor-risk, nivolumab plus ipilimumab provided obvious PFS advantage over sunitinib (HR 0.57; 95% CI 0.4-0.70). For PFS, there was a 41.7% likelihood that sunitinib was the preferred treatment for favorable-risk patients. There was a 38.3% likelihood that cabozantinib was the preferred option for intermediate-risk patients. There was a 67.7% chance that nivolumab plus ipilimumab was the best therapy for poor-risk patients. There were no significant differences in the rate of drug-related adverse events.

Conclusion: Sunitinib, cabozantinib, and nivolumab plus ipilimumab might be the optimum treatments for advanced/metastatic RCC of favorable-risk, poor-risk, and poor-risk, respectively.

Keywords: renal cell carcinoma; systemic therapies; risk stratification; efficacy; safety.

1. Introduction

Renal cell carcinoma (RCC) comprises approximately 90% of renal cancer, and represents approximately 2-3% of all new cancers worldwide [1]. It was estimated that there would be 62 700 new cases of renal cancer and 14 240 renal cancer-related deaths in the United States in 2016 [2]. In the European Union, new renal cancer cases and deaths in 2012 were approximately 84 400 and 34 700, respectively [3]. Up to 30% of patients present with advanced/metastatic RCC at the time of initial diagnosis [4, 5]. Advanced/metastatic RCC is not a single condition, but is actually a heterogeneous group of conditions with different prognosis. The most widely accepted prognostic model is from the Memorial Sloan Kettering Cancer Center (MSKCC) and stratifies patients into favorable-, intermediate-, and poor-risk groups depending on the existence of well-characterized laboratory and clinical risk factors. The 2-year survival rates were 45%, 17%, and 3% for favorable-, intermediate-, and poor-risk groups, respectively [6]. In this systematic review, we focus on favorable-, intermediate-, and poor-risk patients with advanced/metastatic RCC.

In recent years, systemic treatment for advanced/metastatic RCC has changed from cytokines to drugs targeting angiogenesis. To date, eight targeted drugs have been approved for treating advanced/metastatic RCC both in USA and Europe: five tyrosine kinase inhibitors (TKIs): sunitinib, sorafenib, pazopanib, cabozantinib, and axitinib; two mammalian target of rapamycin (mTOR) complex 1 kinase inhibitors: temsirolimus, and everolimus; and the recombinant humanized antivascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab combined with interferon-α (IFN-α). All eight targeted drugs showed significant survival benefit in randomized trials and established a prominent role in treating advanced/metastatic RCC [7-14]. More recently, immune checkpoint antibodies have introduced a new treatment option. CheckMate 214 reported that nivolumab plus ipilimumab was associated with a significantly higher overall survival than sunitinib in the first-line setting [15]. To further improve their efficacy, the combination of different classes of agents is currently evaluated in clinical trials [16-19]. However, there are insufficient

head-to-head RCTs to directly investigate the comparative effectiveness of all available therapies. Given the variety of treatment options for patients advanced/metastatic RCC and the limited evidence regarding the optimum treatment strategy, it is a challenge for clinicians to make the best decision.

A previous meta-analysis was attempted to investigate the comparative effects of different systemic agents for treatment of advanced/metastatic RCC [20]. However, trials included in the systematic review enrolled patients with different risk groups. The analysis used aggregate data and did not perform subgroup analysis based on risk strata. In the present study, we performed a Bayesian network meta-analysis to compare first-line systemic treatments for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively. Network meta-analysis enables indirect comparisons based on a common comparator treatment when a head-to-head trial is unavailable and integrates direct and indirect comparisons to compare several treatment strategies while fully respecting randomization [21, 22]. We aimed to summarize and compare the efficacy and safety associated with currently available systemic therapies for treating advanced/metastatic RCC of different risk categories using network meta-analysis.

2. Methods

2.1. Literature-search strategy

A comprehensive literature search was performed in Pubmed, Web of Science, ClinicalTrials.gov, and Cochrane databases for RCTs of systemic therapies of advanced/metastatic RCC (appendix for all search terms). All the reference lists of identified trials and related reviews were examined to find potential trials. The search was conducted in September 2019. There were no publication date or language restrictions.

2.2. Inclusion and exclusion criteria

All studies were selected according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria[23]. Studies were

included if they satisfied three criteria: (1) the study enrolled patients who had histologically or cytologically confirmed advanced/metastatic RCC of favorable-, intermediate-, or poor-risk; (2) patients were randomly assigned to receive systemic therapies alone or in combination. Relevant interventions included, but were not restricted to: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab, ipilimumab, axitinib, tivozanib, everolimus, temsirolimus, bevacizumab, IFN-α or IL-2. Previous systemic therapy for advanced/metastatic RCC was not allowed; (3) one or more of the outcomes of interest mentioned below were reported. Nonoriginal articles, duplicate reports and non-RCTs were excluded.

2.3. Data Extraction and Quality Assessment

Two researchers (GH. Cao and XQ. Wu) examined the manuscripts of included trials independently, and extracted data into a structured form, including patient characteristics, treatment strategies, and interest outcomes [PFS, high-grade (grade ≥ 3) and overall drug-related adverse events]. Data were extracted from intention-to-treat analyses as far as possible. The methodological quality of included RCTs was assessed using the Cochrane risk of bias assessment tool [24]. Disagreement between investigators was resolved by consensus.

2.4. Data synthesis and analysis

First, we performed traditional meta-analyses to compare the treatments using Stata v.12 (StataCorp, College Station, TX, USA). We applied the chi-square test and the I^2 statistic to investigate the possibility of heterogeneity among studies. A P value < 0.10 or an I2 > 50% suggested the presence of substantial heterogeneity.

Second, we did Bayesian network meta-analyses. For meta-analysis of PFS, the reported adjusted hazard ratios (HRs) with 95% CIs were applied as the outcome measure. For studies not reporting HRs, we calculated them employing the pragmatic approach reported by Tierney et al [25]. For drug-related adverse events, we calculated odds ratios (ORs) of every trial for meta-analysis. Both random-effects and fixed-effects models were performed for the analyses [26]. Goodness of model fit was

assessed using the deviance information criterion and between-study standard deviation [26, 27]. Convergence was determined graphically according to the method described by Gelman *et al* [28].

It is believed that certain systemic treatments are effective in certain risk groups than others, for example sunitinib is more effective in favorable-risk patients and nivolumab plus ipilimumab is more effective in intermediate and poor-risk patients [29], suggesting that there is a treatment-by-risk group (favorable-, intermediate-, and poor-risk groups) interaction. Taking no account of this possible interaction in the analysis, we suppose the transitivity assumption across all included trials would be violated. Consequently, we performed all network analyses separately by risk groups (favorable-, intermediate-, and poor-risk groups) according to the MSKCC risk model .

One key assumption for network analysis is that direct and indirect comparisons do not disagree beyond chance [26, 30, 31]. To explore for evidence of inconsistency in the network, investigators compared the estimated treatment effects from the entire network with traditional pair-wise estimates [31]. Sensitivity analyses were performed restricted to trials that assessed approved systemic therapies. Publication bias and small-study effects were assessed using funnel plots [32].

We performed the Bayesian network analysis using OpenBUGS version 3.2.2 for PFS, and Gemtc version 0.14.3 (van Valkenhoef *et al*, 2012) for adverse events. For PFS, we applied 15 000 iterations obtained after a training phase of 10 000-iteration. In order to minimize autocorrelation, we applied a thinning interval of 50 for each chain. For adverse events, we applied the 60 000 iterations after a training phase of 40 000 iterations.

3. Results

3.1. Search results and study characteristics

The literature search yielded 1 733 potentially eligible studies, of which 1 625 were excluded based on screening titles and abstracts (Fig. 1). The full text of 108

remaining studies were analyzed, and finally 19 publications reporting 13 unique RCTs were included (Table), involving 7 248 participants randomly assigned to one of the 11 treatment strategies: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab plus ipilimumab, axitinib, tivozanib, everolimus, IFN-α, bevacizumab plus IFN-α, and temsirolimus plus bevacizumab. According to the MSKCC criteria, there were 2 318, 4 413 and 517 participants had favorable-, intermediate-, and poor-risk disease, respectively.

The main characteristics of included RCTs are summarized in Table. The demographic characteristics of patients were well balanced across trials. Enrolled patients across trials were similar in terms of age, gender, and risk classification. Across trials, the median age of patients ranged from 58 to 64 years. The participants were predominantly male (71%, 5 163 of 7 248). The included trials were designed similarly. Median follow-up ranged from 18.75 to 58 months. The mean sample sizes were 105, 184 and 37 patients per group for favorable-, intermediate- and poor-risk subtypes, respectively. 11 trials selected for clear-cell carcinoma subtypes [8-10, 14, 15, 33-38], and two trials also included small subsets of non-clear-cell histotypes, each comprising 11% and 14% of the study population, respectively [39, 40]. All studies were two-arm trials. The dosages used in most of trials were within the recommended dose ranges.

In this network meta-analysis, results are reported based on fixed-effects models because they demonstrated better goodness of fit compared with random-effects models. The results of random-effects models are available in appendix Table 1-5.

3.2. Progression-free survival

3.2.1. For advanced/metastatic RCC of favorable-risk, 11 trials enrolling 2 318 total patients reported adequate information on progression-free survival and contributed to network meta-analysis (Fig. 2A) [8-11, 14, 15, 34-37, 39, 40]. Fig. 2B summarises the results of the network meta-analysis for PFS. Compared with sunitinib, IFN-α, temsirolimus plus bevacizumab, and nivolumab plus ipilimumab were associated with significantly worse PFS (HR 2.70, 95% CI 1.59-4.51; HR 1.96, 95% CI 1.04-3.63;

and HR 1.56, 95% CI 1.32-1.84, respectively). Based on the analysis of SUCRA, there was a 41.7% chance that sunitinib provided the greatest PFS benefit for patients with favorable-risk disease (Fig. 2C).

3.2.2. For advanced/metastatic RCC of intermediate-risk, 12 trials enrolling 4 413 total patients contributed to the analysis of PFS (Fig. 3A) [8-11, 14, 15, 33-37, 40]. Network meta-analysis demonstrated that nivolumab plus ipilimumab and cabozantinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.66, 95% CI 0.54-0.81; HR 0.64, 95% CI 0.43-0.96, respectively). Temsirolimus plus bevacizumab, and bevacizumab plus IFN-α were significantly less efficacious for PFS than sunitinib (HR 1.85, 95% CI 1.21-2.81; HR 1.68, 95% CI 1.18-2.40) (Fig. 3B). Based on the analysis of SUCRA, cabozantinib was most likely to be the best treatment for intermediate-risk patients. Nivolumab plus ipilimumab was likely to be second-best treatment, while axitinib and tivozanib had a similar likelihood of being the third-best option for patients with intermediate-risk disease (Fig. 3C).

3.2.3. Based on data that was available for advanced/metastatic RCC of poor-risk, the network involved seven trials comparing seven different treatments (517 total patients; Fig. 4A) [14, 15, 33-35, 37, 40]. Network meta-analysis demonstrated that only nivolumab plus ipilimumab was associated with a significantly higher improvement in PFS than sunitinib (HR 0.57; 95% CI 0.4-0.70)(Fig. 4B). On SUCRA-based analysis, there was a 67.7% probability that nivolumab plus ipilimumab had the greatest PFS for poor-risk patients (Fig. 4C)

3.3. Adverse events

Seven trials contributed to our analysis of overall and high-grade drug-related adverse events [8, 9, 11, 14, 15, 36, 39]. All the seven trials did not provide adverse events data for different risk groups, so we extracted a summary of adverse event data. Results of comparisons of adverse events of seven systemic treatments are presented

in Fig. 5 and appendix Fig. 1 Stepwise comparison of all the seven therapies did not find significant differences in rates of high-grade or overall adverse events.

3.4. Network assumptions, sensitivity analysis, publication bias, and risk of bias

Consistencies between direct and indirect evidence were noted for any comparisons (Fig. 6 and appendix Table 1-5). Results from the sensitivity analyses were in line with the primary analysis (appendix Table 6).The comparison-adjusted funnel plot (Fig. 7) for PFS was largely symmetric, indicating no obvious small-study effects and publication bias. The methodological quality was moderate in the included studies (appendix Fig. 2). All trials were thought to have low risk of bias for random sequence generation, incomplete outcome data, and selective reporting of outcomes. Eight trials had evidence of high risk of bias for masking [10, 11, 14, 35-37, 39, 40].

4. Discussion

Our network meta-analysis of 13 RCTs including 7 248 individuals assessed the efficacy and safety of all major systematic therapies for the treatment of advanced/metastatic RCC in the first-line setting. Findings of this meta-analysis might help to choose among systemic agents for the management of patients with previously untreated advanced/metastatic RCC. For advanced/metastatic RCC of favorable-risk, sunitinib was most likely to be the best treatment regimen. For patients with intermediate-risk, cabozantinib seemed to be the most efficacious treatment strategy. For poor-risk patients, nivolumab plus ipilimumab provided obvious PFS advantages over other treatments. In terms of drug-related adverse events, there were no significant differences among systemic therapies.

In RCC with clear cell subtype, hypoxia-inducible factor (HIF) accumulation due to loss of von Hippel-Lindau (VHL) leads to overexpression of VEGF and platelet derived growth factor (PDGF), which promotes tumor angiogenesis [41-43]. This process substantially makes a contribution to the development and progression of clear cell RCC. Inhibiting the VEGF signaling has been supposed as the key mechanism for antitumor effects in clear cell RCC. To date, eight targeted drugs have

been approved for treating advanced RCC: sunitinib, sorafenib, pazopanib, cabozantinib, axitinib, everolimus, temsirolimus, and bevacizumab (in combination with IFN-α).

As shown in this analysis, for patients with intermediate-risk, sunitinib resulted in a significant PFS benefit compared with everolimus. The varied clinical benefit could be associated with mechanisms of action of TKI and mTOR inhibitor. Sunitinib not only inhibit VEGF receptors -1, -2, and -3, which may be the most clearly relevant targets in RCC so far, but also exhibit potent activity against PDGF receptor [9, 44]. It has been reported that PDGF plays a critical role in the recruitment of pericytes to sprouting tumor vessels, and pericyte-covered vessels are more likely resistant to anti-vascular therapy than those pericyte-negative vessels [45, 46]. The mTOR complex is the upstream of an intracellular signaling network regulating cell growth and angiogenesis, and it plays a key role in the pathogenesis of advanced/metastatic RCC [47]. It has been demonstrated that rapamycin analogs, including everolimus and temsirolimus, inhibit only one of two signaling complexes of mTOR [48]. The mTORC1 signaling is potently inhibited by everolimus and temsirolimus, while the mTORC2 signaling is not [49]. Consequently, one downstream signaling of mTOR activation is unopposed. The relatively unsatisfactory efficacy should disable the mTOR inhibitors as more suitable therapies for the treatment of advanced/metastatic RCC than TKIs. Regarding TKIs, our results suggest that sunitinib was most likely to be the best treatment regimen for patients with favorable-risk disease.

A potentially additive benefit from combinations of targeted drugs has been suggested on the basis that they inhibit separate cellular pathways. However, our results show that temsirolimus plus bevacizumab, and bevacizumab plus IFN-α provide little survival benefit compared with sunitinib, further confirming absence of evidence that combination treatment simultaneously inhibiting both VEGF and mTOR signaling results in therapeutic synergy [17, 19, 37, 50, 51].

For patients with intermediate-risk, cabozantinib seemed to be the most efficacious treatment strategies. Our study results show that cabozantinib demonstrates clinical superiority over sunitinib among patients with intermediate-risk. The benefit of

cabozantinib over sunitinib may reflect the target tyrosine kinases of cabozantinib, which includes AXL and MET in addition to VEGF receptors. It is reported that upregulated AXL or MET is closely related to resistance to VEGF receptor inhibitors and poor prognosis in several cancer models [52-55]. Therefore, targeting these two oncoproteins in addition to VEGF receptors may provide further antitumor effects in RCC than more selective VEGF receptors targeted agents.

Immune checkpoint antibodies block the inhibitory T-cell receptor programmed death-1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4)-signaling to augment tumor specific immune response [56]. Nivolumab (an anti-PD-1 antibody) is approved for the treatment of advanced RCC in the second line setting. Ipilimumab (an anti- CTLA-4 antibody) is approved for the treatment of advanced melanoma. Nivolumab plus ipilimumab has been reported significant efficacy in multiple tumor types [57-60].

In this analysis, nivolumab plus ipilimumab was associated with a significant PFS advantage compared with sunitinib among intermediate- and poor-risk patients. In contrast, sunitinib was associated with a significantly longer PFS than nivolumab plus ipilimumab among favorable-risk patients. The inconsistent results of the comparison between nivolumab plus ipilimumab and sunitinib may be explained by different mechanisms of action. It's reported that immunotherapy might be associated with "pseudo-progression" phenomenon according to the (Response Evaluation Criteria in Solid Tumors) RECIST criteria [61, 62]. For instance, in a subgroup analysis of the CheckMate 025 trial comparing nivolumab with everolimus for mRCC in second-line setting, 69% patients treated beyond progression demonstrated sustained tumor reduction or target lesion stabilization [63]. As such, no significant PFS results in immunotherapy clinical trials are understandable, and this different mechanism of action likely explains inconsistent results of nivolumab plus ipilimumab compared with sunitinib. Regardless of the mechanism, these results highlight the need to better understand the biologic mechanisms of different treatment regimens. Combinations of immune therapy with targeted therapy may provide the best opportunity to maximize survival benefit [64].

There are several factors which make an analysis of OS challenging, therefore meta-analysis on OS was not performed. First, the OS data were not reported in five included studies. Second, for the available OS data, there were issues of confounders, such as crossover to more efficacious treatment and the influence of subsequent anticancer therapies [33, 36, 65]. These factors can substantially underestimate the difference between two treatments in terms of OS. In addition, PFS has been recognized as a surrogate endpoint of OS in medical oncology as well as in advanced/metastatic RCC in the TKI era [66].

The strengths of our study are as follows. To the best of our knowledge, this study is the first network analysis to compare systemic treatments for advanced/metastatic RCC separately by risk groups. We applied multiple rigorous search strategies to retrieve all potentially eligible RCTs. In the present study, we comprehensively compared and ranked all available first-line systemic therapies for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively, thus providing physicians with an overall appraisal of systemic therapies for different risk groups. In addition, we used Bayesian network meta-analysis to synthesize data. This approach provides indirect effect estimates in the absence of head-to-head trial and incorporates all available information from RCTs while fully maintaining randomization [21, 22]. We applied various statistical models to increase reliability of the results. Results were consistent across all analyzed outcomes. Moreover, the reliability and accuracy of results were corroborated by the low statistical heterogeneity and excellent model fit. Finally, assessment of both efficacy and adverse events provides new insights into the benefit-harm balance of different systemic treatments.

However, the limitations of our study must be taken into account. The major limitation of this network meta-analysis lies in the reporting quality of trials reviewed. Eight included trials were not masked, which might affect the validity of our findings. Moreover, this meta-analysis was conducted based on summary statistics rather than individual patient level data. There might be some confounding factors (*e.g.*, ethnic origin, prior nephrectomy, *etc*.) at the individual patient level that might influence the

benefit of systemic treatments, but were not available; therefore analyses adjusted for these factors were impossible in our network meta-analysis. Access to patient-level longitudinal data would allow us to establish more robust and accurate conclusions in specific subgroups of patients. Moreover, the length of follow-up varied across studies, resulting in potential variations in survival benefits of systemic treatments. Due to only five trials reporting median follow-up, sensitivity analyses adjusted for this factor were impossible. Moreover, individual dosage varied across studies and data were too sparse to investigate effects of different schedules, which might somewhat affect the generalisability of our findings. Finally, findings in this meta-analysis were mainly based on patients with clear-cell advanced RCC, thus no robust recommendations can be provided for non-clear-cell subtypes.

5. Conclusions

Our network meta-analysis suggested that: sunitinib might be the optimum treatment for advanced/metastatic RCC of favorable-risk; cabozantinib was most likely to provide the greatest PFS benefit for intermediate-risk patients; nivolumab plus ipilimumab might be the optimum treatments for poor-risk patients. Further well-designed, large-scale RCTs are required to confirm and update the findings of this analysis.

Strengths and limitations of this study

► This is the first network analysis to compare systemic treatments for advanced/metastatic RCC separately by risk groups.

► Various statistical models were applied to synthesize data. The reliability and accuracy of results were corroborated by the low statistical heterogeneity and excellent model fit.

►Assessment of both efficacy and adverse events provides new insights into the benefit-harm balance of different systemic treatments.

►Main limitation lies in the reporting quality of trials included.

Author Contributions

G-HC and X-QW conceived and designed the meta-analysis, J-PW and Z-ZW identified and acquired reports of trials, and extracted data. XW and H-TZ analyzed and interpreted the data. G-PJ contacted authors of trials for additional information. G-HC and X-QW drafted the manuscript. d T-ZY critically reviewed the manuscript. All authors approved the final submitted version of the report.

Fundings: This research was supported by the Henan Provincial Medical Scientific and Technological Research Project (Grant No. 201702191). The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflicts of Interest: None declared.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research.

References:

1. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67(5):913-24.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30.
3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.
4. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am. 2003;30(4):843-52.
5. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med. 2005;353(23):2477-90.
6. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies Against Advanced Renal Cell Carcinoma. Journal of Clinical Oncology. 2002;20(1):289-96.

7. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol. 2008;26(33):5422-8.

8. Negrier S, Jager E, Porta C, McDermott D, Moore M, Bellmunt J, et al. Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. Med Oncol. 2010;27(3):899-906.

9. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061-8.

10. Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol. 2013;14(13):1287-94.

11. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369(8):722-31.

12. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115-24.

13. Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(8):1280-9.

14. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. Journal of Clinical Oncology. 2017;35(6):591-7.

15. Motzer RJ, Tannir NM, McDermott DF, Aren FO, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;378(14):1277-90.

16. Jonasch E, Corn P, Pagliaro LC, Warneke CL, Johnson MM, Tamboli P, et al. Upfront, randomized, phase 2 trial of sorafenib versus sorafenib and low-dose interferon alfa in patients with advanced renal cell carcinoma: clinical and biomarker analysis. Cancer. 2010;116(1):57-65.

17. Negrier S, Gravis G, Perol D, Chevreau C, Delva R, Bay JO, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol. 2011;12(7):673-80.

18. Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: the ROSORC trial. Br J Cancer. 2011;104(8):1256-61.

19. Ravaud A, Barrios CH, Alekseev B, Tay MH, Agarwala SS, Yalcin S, et al. RECORD-2: phase II randomized study of everolimus and bevacizumab versus interferon alpha-2a and bevacizumab as first-line therapy in patients with metastatic renal cell carcinoma. Ann Oncol. 2015;26(7):1378-84.

20. Wallis CJD, Klaassen Z, Bhindi B, Ye XY, Chandrasekar T, Farrell AM, et al. First-line Systemic Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. Eur Urol. 2018;74(3):309-21.

21. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ. 2005;331(7521):897-900.

22. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23(20):3105-24.

23. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151(4):W65-94.

24. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343.

25. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.

26. Dias S, Welton NJ, Sutton AJ, Ades AE. A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. Medical Decision Making. 2014.

27. Spiegelhalter DJ, Best NG, Carlin BP, Der Linde AV. Bayesian measures of model complexity and fit. Journal of The Royal Statistical Society Series B-statistical Methodology. 2002;64(4):583-639.

28. Gelman A, Rubin DB. Markov chain Monte Carlo methods in biostatistics. Stat Methods Med Res. 1996;5(4):339-55.

29. Powles T, Albiges L, Staehler M, Bensalah K, Dabestani S, Giles RH, et al. Updated European Association of Urology Guidelines Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. Eur Urol. 2017;73(3):311-5.

30. Caldwell DM, Welton NJ, Ades AE. Mixed treatment comparison analysis provides internally coherent treatment effect estimates based on overviews of reviews and can reveal inconsistency. J Clin Epidemiol. 2010;63(8):875-82.

31. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making. 2013;33(5):641-56.

32. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One. 2013;8(10):e76654.

33. Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. 2010;28(13):2144-50.

34. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010;28(13):2137-43.

35. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(22):3584-90.

36. Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol. 2013;31(30):3791-9.

37. Rini BI, Bellmunt J, Clancy J, Wang K, Niethammer AG, Hariharan S, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. J Clin Oncol. 2014;32(8):752-9.

38. Motzer RJ, Hutson TE, McCann L, Deen K, Choueiri TK. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. N Engl J Med. 2014;370(18):1769-70.

39. Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, et al. Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): final results of the ROSORC trial. Ann Oncol. 2013;24(12):2967-71.

40. Motzer RJ, Barrios CH, Kim TM, Falcon S, Cosgriff T, Harker WG, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol. 2014;32(25):2765-72.

41. Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med. 2003;349(5):427-34.

42. Patard JJ, Rioux-Leclercq N, Fergelot P. Understanding the importance of smart drugs in renal cell carcinoma. Eur Urol. 2006;49(4):633-43.

43. Costa LJ, Drabkin HA. Renal cell carcinoma: new developments in molecular biology and potential for targeted therapies. Oncologist. 2007;12(12):1404-15.

44. Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res. 2003;9(1):327-37.

45. Benjamin LE, Hemo I, Keshet E. A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF. Development. 1998;125(9):1591-8.

46. Gee MS, Procopio WN, Makonnen S, Feldman MD, Yeilding NM, Lee WM. Tumor vessel development and maturation impose limits on the effectiveness of anti-vascular therapy. Am J Pathol. 2003;162(1):183-93.

47. Creighton CJ, Morgan M, Gunaratne PH, Wheeler DA, Gibbs RA, Gordon Robertson A, et al. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature. 2013;499(7456):43-9.

48. Loewith R, Jacinto E, Wullschleger S, Lorberg A, Crespo JL, Bonenfant D, et al. Two TOR

complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. Mol Cell. 2002;10(3):457-68.

49. Inoki K, Guan KL. Complexity of the TOR signaling network. Trends Cell Biol. 2006;16(4):206-12.

50. Bukowski RM, Kabbinavar FF, Figlin RA, Flaherty K, Srinivas S, Vaishampayan U, et al. Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. J Clin Oncol. 2007;25(29):4536-41.

51. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356(22):2271-81.

52. Gibney GT, Aziz SA, Camp RL, Conrad P, Schwartz BE, Chen CR, et al. c-Met is a prognostic marker and potential therapeutic target in clear cell renal cell carcinoma. Ann Oncol. 2013;24(2):343-9.

53. Gustafsson A, Martuszewska D, Johansson M, Ekman C, Hafizi S, Ljungberg B, et al. Differential expression of Axl and Gas6 in renal cell carcinoma reflecting tumor advancement and survival. Clin Cancer Res. 2009;15(14):4742-9.

54. Ciamporcero E, Miles KM, Adelaiye R, Ramakrishnan S, Shen L, Ku S, et al. Combination strategy targeting VEGF and HGF/c-met in human renal cell carcinoma models. Mol Cancer Ther. 2015;14(1):101-10.

55. Zhou L, Liu XD, Sun M, Zhang X, German P, Bai S, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. 2016;35(21):2687-97.

56. Ribas A. Tumor immunotherapy directed at PD-1. N Engl J Med. 2012;366(26):2517-9.

57. Hammers HJ, Plimack ER, Infante JR, Rini BI, McDermott DF, Lewis LD, et al. Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. J Clin Oncol. 2017;35(34):3851-8.

58. Antonia SJ, Lopez-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016;17(7):883-95.

59. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31-41.

60. Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(13):1270-1.

61. West HJ. JAMA Oncology Patient Page. Immune Checkpoint Inhibitors. JAMA Oncol. 2015;1(1):115.

62. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15(23):7412-20.

63. George S, Motzer RJ, Hammers HJ, Redman BG, Kuzel TM, Tykodi SS, et al. Safety and Efficacy of Nivolumab in Patients With Metastatic Renal Cell Carcinoma Treated Beyond Progression: A Subgroup Analysis of a Randomized Clinical Trial. JAMA Oncol. 2016;2(9):1179-86.

64. Atkins MB, Plimack ER, Puzanov I, Fishman MN, McDermott DF, Cho DC, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncol. 2018;19(3):405-15.

65. Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer. 2013;49(6):1287-96.

66. Halabi S, Rini B, Escudier B, Stadler WM, Small EJ. Progression-free survival as a surrogate endpoint of overall survival in patients with metastatic renal cell carcinoma. Cancer. 2014;120(1):52-60.

Table: Studies included in the multiple-treatments meta-analysis

Study	Number of patients	Age (years) median(range)	Sex (% male)	MSKCC (%)			Median PFS in months (95% CI)	Hazard ratio (95% CI)
				Favorable	Intermediate	Poor		
Motzer 2014 (RECORD-3)								
Everolimus	238	62 (20-89)	69.7	29	56	15	7.9	1.4 (1.2-1.8)
Sunitinib	238	62 (29-84)	73.9	30	56	14	10.7	1 (Ref)
Motzer 2014 (COMPARZ)								
Pazopanib	557	61 (18-88)	71	27	58	12	8.4 (8.3-10.9)	1.05 (0.90-1.22)
Sunitinib	553	62 (23-86)	75	27	59	9	9.5 (8.3-11.1)	1 (Ref)
Rini 2014 (INTORACT)								
Temsirolimus plus bevacizumab	400	59 (22-87)	72	28	65	8	9.1 (8.1-10.2)	1.1 (0.9-1.3)
Bevacizumab plus IFN-α	391	58 (23-81)	69	27	65	8	9.3 (9.0-11.2)	1 (Ref)
Procopio 2013 (ROSORC)								
Sorafenib plus interleukin-2	66	64 (57-69) *	79	55	41	5	NA	NA
Sorafenib	62	62 (52-69) *	69	55	39	6	NA	NA
Hutson 2013								
Axitinib	192	58 (23-83)	70	49	44	4	10.1 (7.2-12.1])	0.77 (0.56-1.05)
Sorafenib	96	58 (20-77)	77	55	42	2	6.5 (4.7-8.3)	1 (Ref)
Motzer 2013								
Tivozanib	260; treatment-naive 181	59 (23-83)	71	27	67	7	12.7 (9.1-15.0)	0.756 (0.580-0.985)
Sorafenib	257; treatment naive 181	59 (23-85)	74	34	62	4	9.1 (7.3-10.8)	1 (Ref)
Sternberg 2010 (VEG105192)								
Pazopanib	290; treatment naive 155	59 (28-82)	68	36	56	4	11.1	0.40 (0.27-0.60)
Placebo	n = 145; treatment naive 78	62 (25-81)	74	40	51	6	2.8	1 (Ref)
Motzer 2009								
Sunitinib	375	62 (27-87)	71	38	56	6	11 (11-13)	0.539 (0.451-0.643)
IFN-α	375	59 (34-85)	72	34	59	7	5 (4-6)	1 (Ref)
Negrier 2010 (TARGET)								
Sorafenib	451; treatment-naive 77	60	63.6	53.2	46.8	0	5.8	0.48 (0.32-0.73)
Placebo	452; treatment-naive 84	60.5	69	45.2	54.8	0	2.8	1 (Ref)
Rini 2010 (CALGB 90206)								
Bevacizumab plus IFN-α	369	61 (56-70)	73	26	64	10	8.5 (7.5-9.7)	0.71 (0.61-0.83)
IFN-α	363	62 (55-70)	66	26	64	10	5.2 (3.1-5.6)	1 (Ref)

Escudier 2010 (AVOREN)								
Bevacizumab plus IFN-α	327	61 (30–82)	68	27	56	9	10.2	0·61 (0·51-0·73)
IFN-α	322	60 (18–81)	73	29	56	8	5.4	1 (Ref)
								Continued
Motzer 2018 (CheckMate 214)								
Nivolumab plus Ipilimumab	550	62 (26-85)	75	23	61	17	11.6 (8.7–15.5)	0.82(0.64-1.05)‡
Sunitinib	546	62 (21-85)	72	23	61	16	8.4 (7.0–10.8)	1 (Ref)
Choueiri 2017								
Cabozantinib	79	63 (40-82)	83.5	0	81.0§	19.0§	8.2 (6.2 to 8.8)	0.66 (0.46-0.95)
Sunitinib	78	64(31-87)	73.1	0	80.8§	19.2§	5.6 (3.4 to 8.1)	1 (Ref)

IFN-α = interferon-α; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; CI = confidence interval; AE = adverse event; NA=not available; Ref = reference group (hence hazard ratio set to 1);

* interquartile range; † mean; ‡ 99.1% CI; § IMDC risk group, International Metastatic Renal Cell Carcinoma Database Consortium

Figures

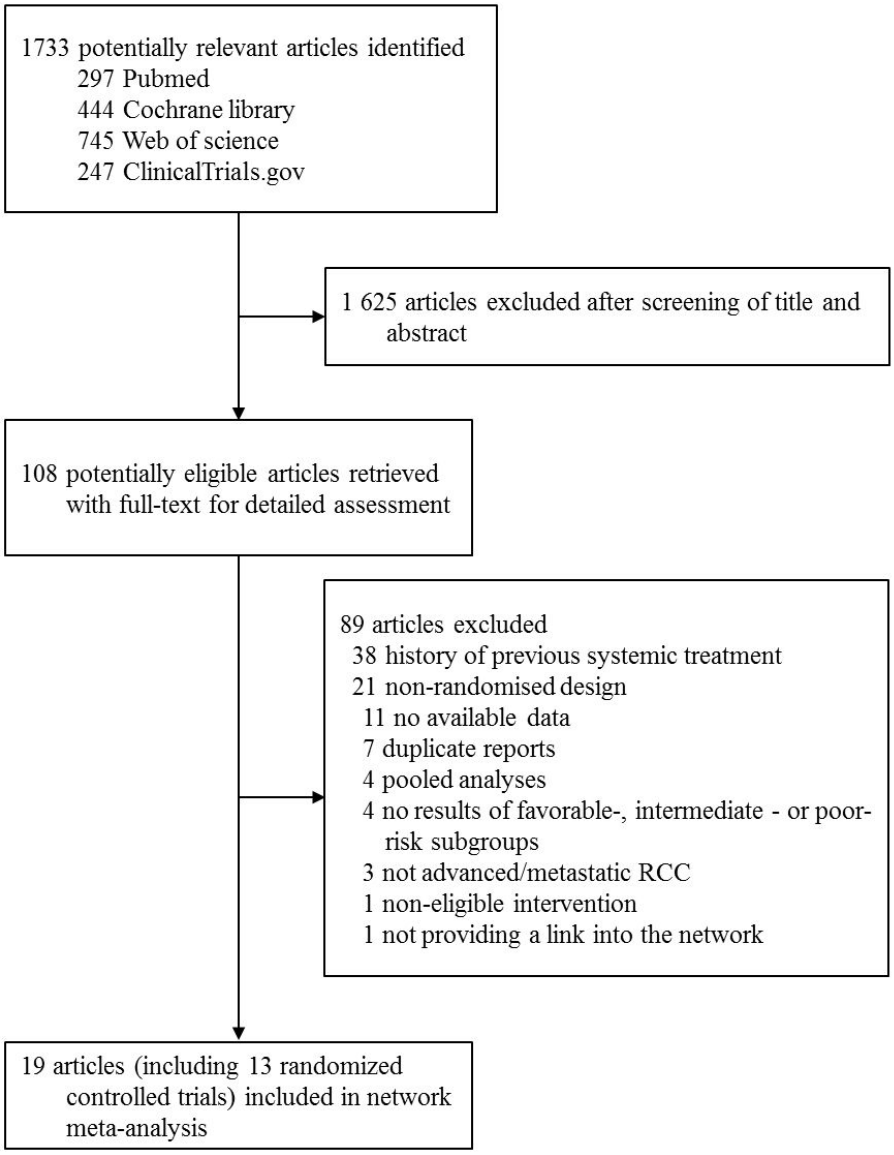


Fig. 1 - Literature search and selection

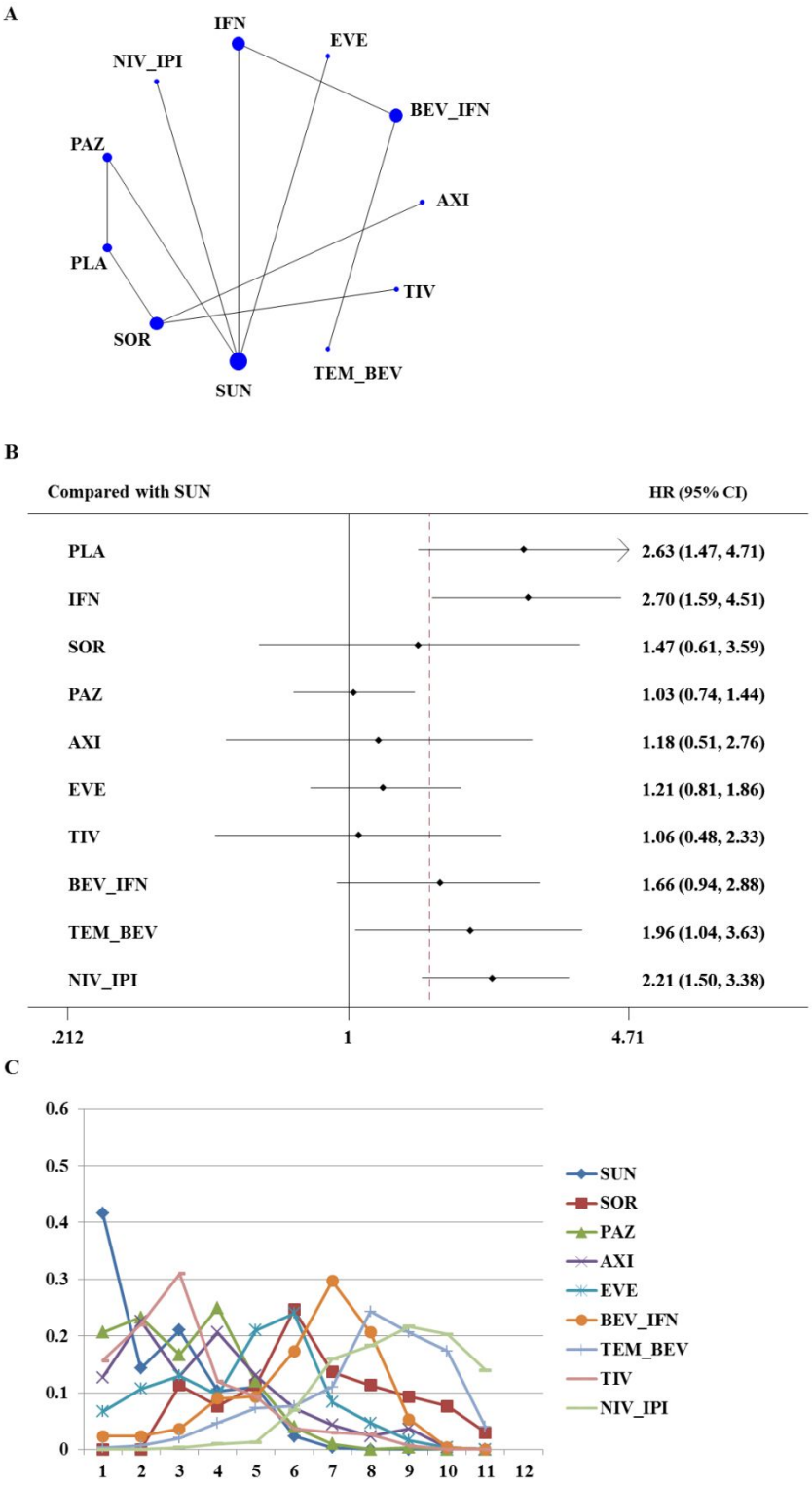


Fig. 2 - Analysis of progression-free survival for patients with favorable-risk disease. (A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) forest plot, with sunitinib as the comparator; (C) SUCRA plot.

HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab.

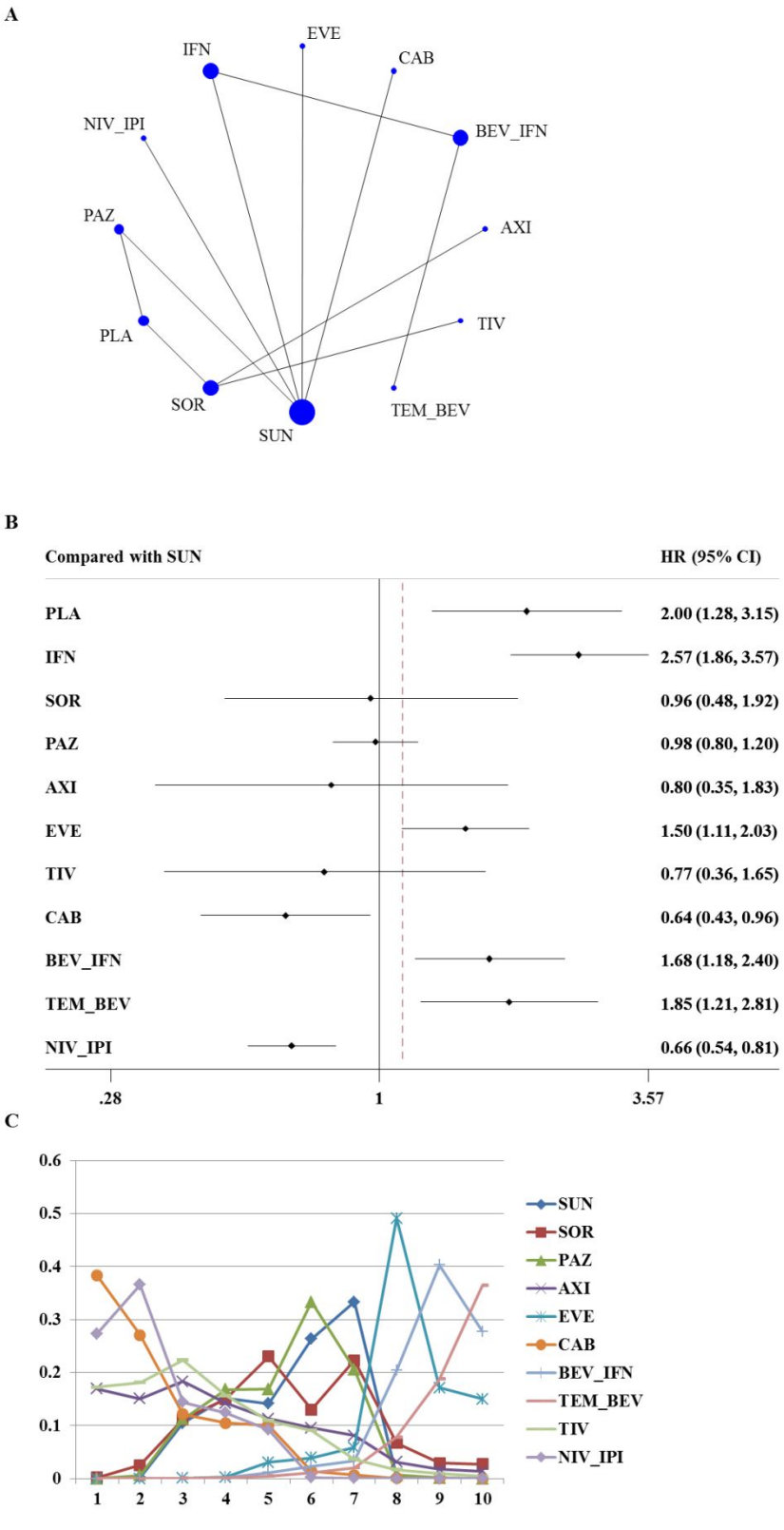


Fig. 3 - Analysis of progression-free survival for patients with intermediate-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C)

SUCRA plot.

HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab.

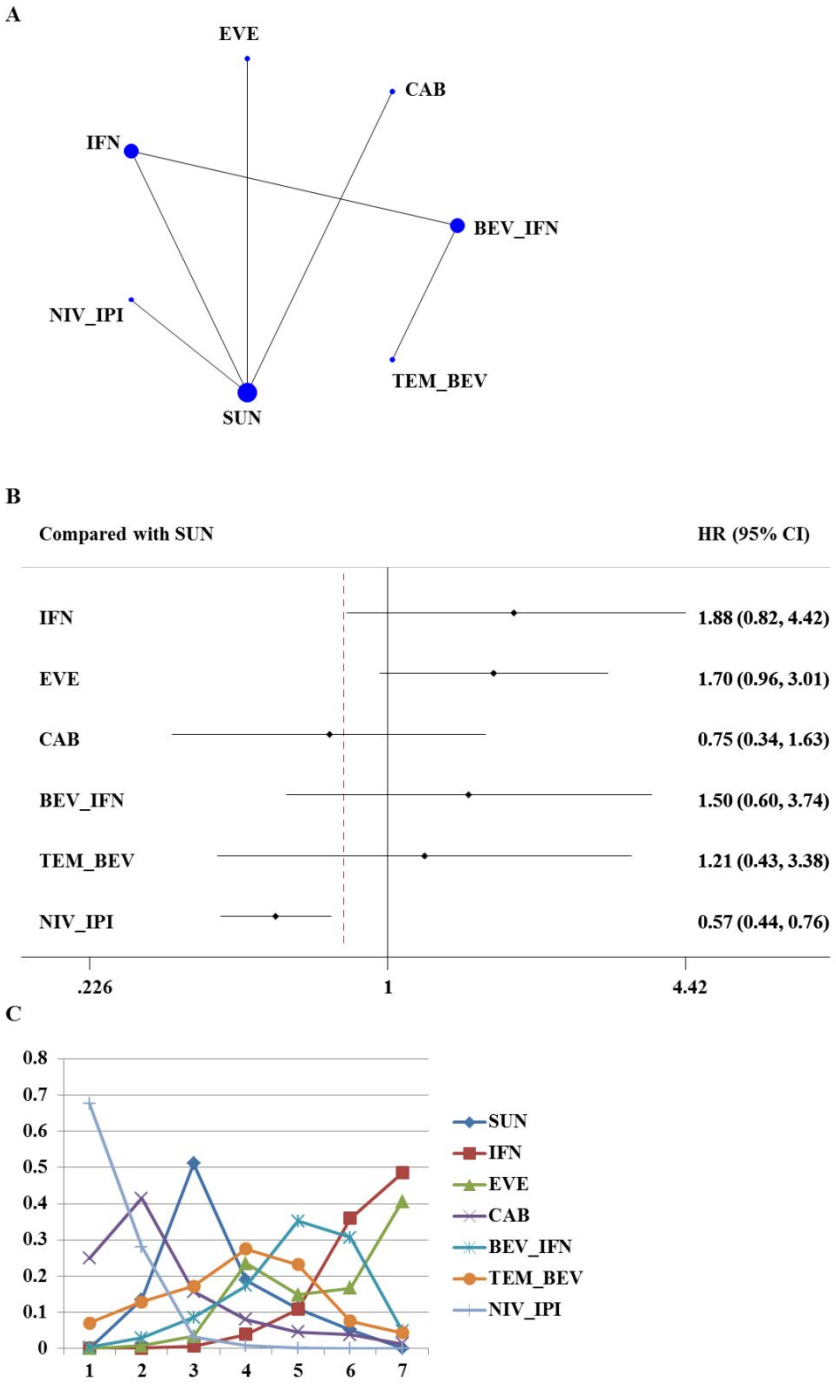


Fig. 4 - Analysis of progression-free survival for patients with poor-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) SUCRA plot.

HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon-α. EVE = everolimus. CAB =

cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab.

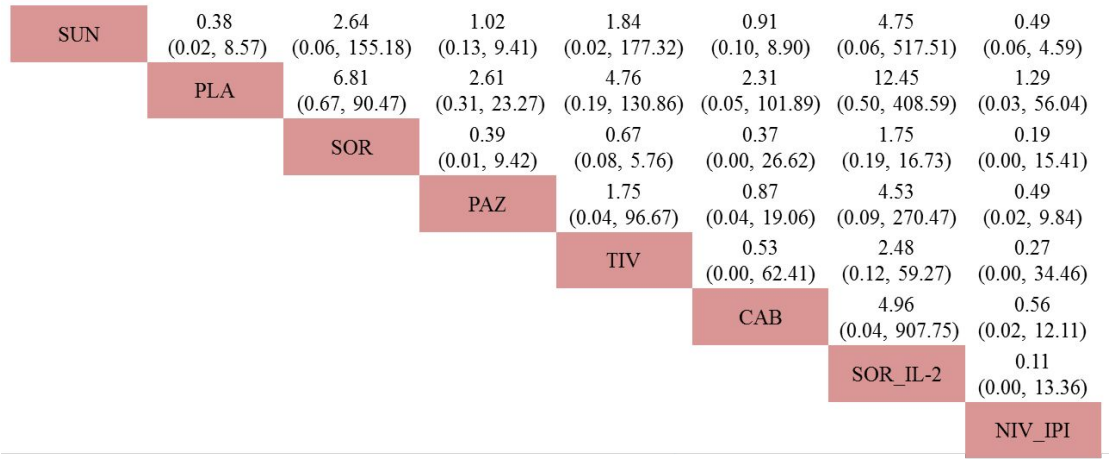


Fig. 5 - Pooled odds ratios for high-grade adverse events.

The column treatment is compared with the row treatment. Odds ratios lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI = nivolumab plus ipilimumab. Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

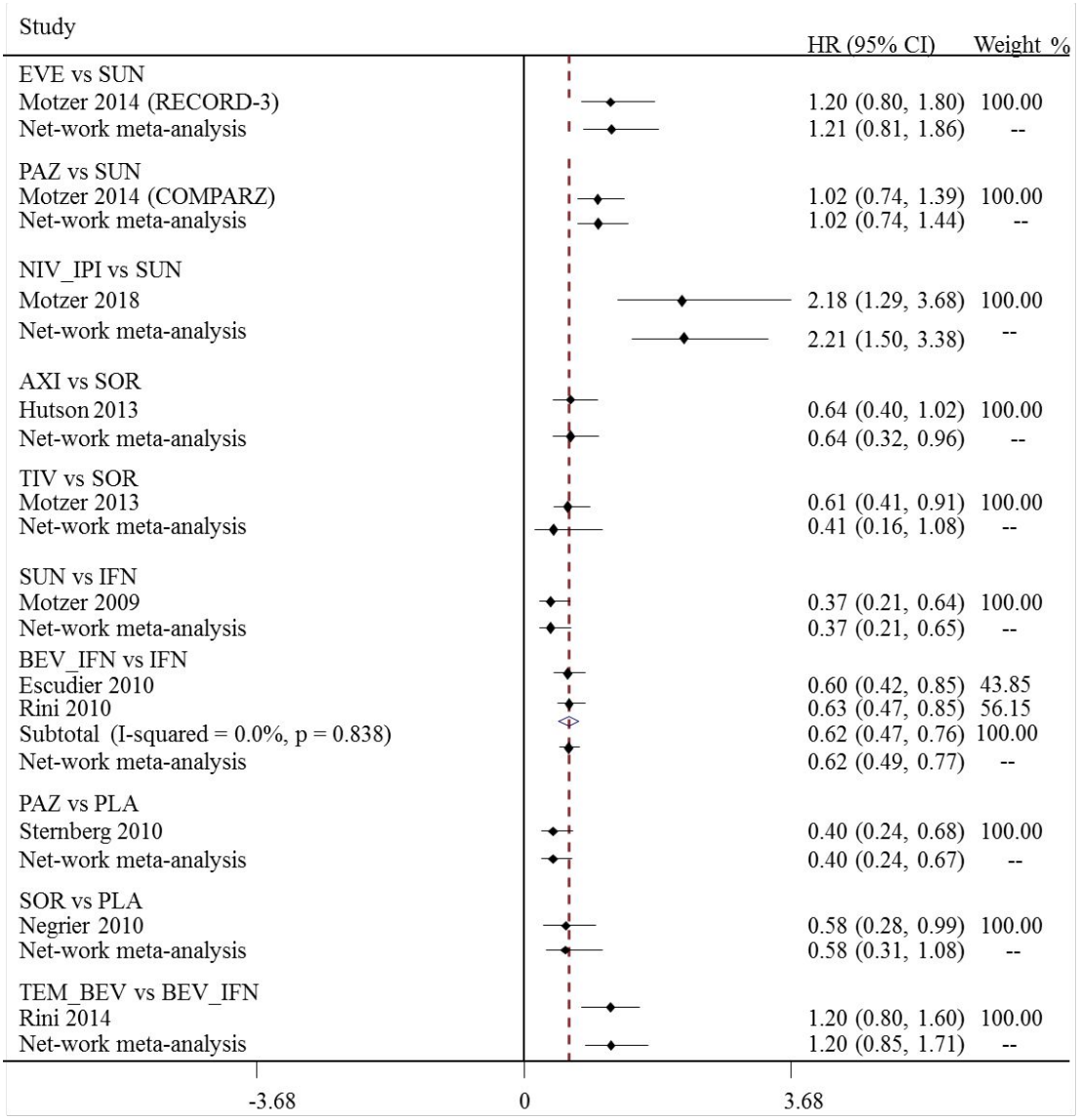


Fig. 6 - Pooled hazard ratios for progression-free survival by Bayesian network-analysis and traditional meta-analysis

HR = hazard ratio. CI=confidence interval for traditional meta-analysis and credible interval for Bayesian network meta-analysis. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab.

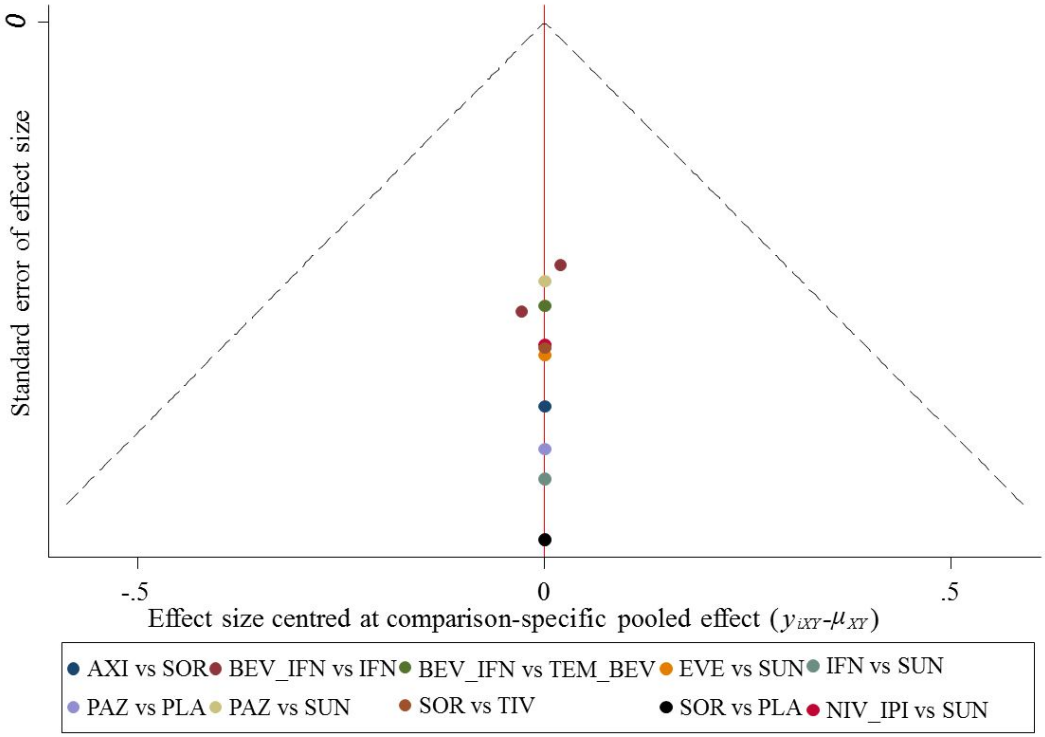


Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis for hazard ratios of progression-free survival

SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab.

Appendix

Search strategy

Pubmed:

((((((((((((sorafenib[Title/Abstract]) OR sunitinib[Title/Abstract]) OR bevacizumab[Title/Abstract]) OR pazopanib[Title/Abstract]) OR temsirolimus[Title/Abstract]) OR everolimus[Title/Abstract]) OR axitinib[Title/Abstract]) OR Cabozantinib[Title/Abstract]) OR IFN-alpha[Title/Abstract]) OR IL-2[Title/Abstract]) OR Nivolumab[Title/Abstract]) OR Immune checkpoint blockade[Title/Abstract])) AND (("Carcinoma, Renal Cell"[Mesh]) OR ((((renal cancer[Title]) OR renal carcinoma[Title]) OR kidney cancer[Title]) OR kidney carcinoma[Title]))
Filter: Controlled Clinical Trial

Cochrane Library:

#1 sorafenib:ti,ab,kw or sunitinib:ti,ab,kw or bevacizumab:ti,ab,kw or temsirolimus:ti,ab,kw or pazopanib:ti,ab,kw (Word variations have been searched)

#2 everolimus:ti,ab,kw or afatinib:ti,ab,kw or cabozanitinb:ti,ab,kw or IFN:ti,ab,kw or IL-2:ti,ab,kw (Word variations have been searched)

#3 nivolumab:ti,ab,kw or Immune checkpoint blockade:ti,ab,kw (Word variations have been searched)

#4 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees

#5 #1 or #2 or #3

#6 #4 and #5, Filter: Trials

Web of science

1 ((((((((((Topic: (sorafenib) OR Topic: (sunitinib)) OR Topic: (bevacizumab)) OR Topic: (pazopanib)) OR Topic: (temsirolimus)) OR Topic: (everolimus)) OR Topic: (afatinib)) OR Topic: (cabozanitinb)) OR Topic: (IFN)) OR Topic: (IL-2)) OR Topic: (nivolumab)) OR Topic: (Immune checkpoint blockade))

2 Title: (renal cell carcinoma) OR Title: (renal cancer) OR Title: (renal carcinoma) OR Title: (kidney cancer) OR Title: (kidney carcinoma)

3 #2 AND #1

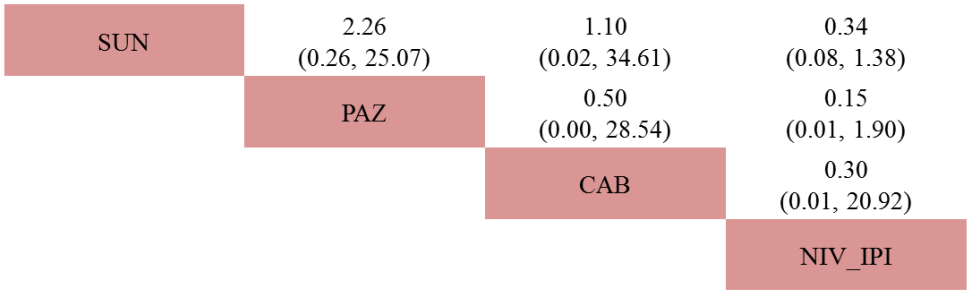
4 #2 AND #1 Document Types: CLINICAL TRIAL

ClinicalTrials.gov:

Category: “renal cell carcinoma OR renal cancer OR renal carcinoma OR kidney cancer OR kidney carcinoma, Studies With Results”

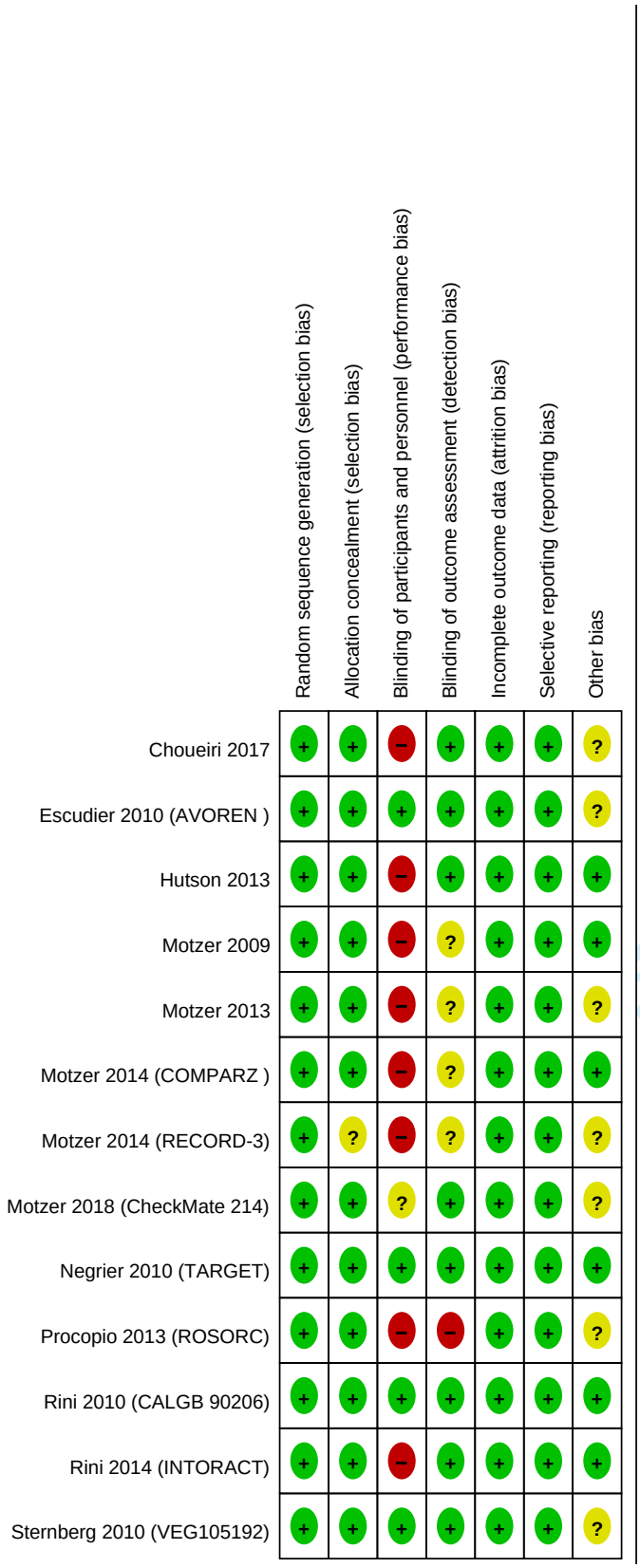
(http://clinicaltrials.gov/)

Appendix figure 1: Pooled odds ratios for **overall adverse events** by Bayesian network meta-analysis



The column treatment is compared with the row treatment. ORs lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. Stepwise comparison of treatments did not find significant differences in rates of overall adverse events. SUN = sunitinib. PAZ = pazopanib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab.

Appendix figure 2: Cochrane risk of bias tool assessment



Appendix Table 1: For advanced/metastatic RCC of favorable-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
PLA	**2.63 (1.47-4.71)**	2.79 (0.005-4812)
IFN	**2.70 (1.59-4.51)**	2.57 (0.05-18.24)
SOR	1.47 (0.61-3.59)	1.56 (0.001-2735)
PAZ	1.03 (0.74-1.44)	1.03 (0.05-142.4)
AXI	0.98 (0.36-2.76)	0.95 (0.001-22200)
EVE	1.21 (0.81-1.86)	1.28 (0.03-66.05)
BEV_IFN	1.66 (0.94 -2.88)	1.54 (0.01-24.08)
TEM_BEV	**1.96 (1.04 -3.63)**	1.92 (0.02-155.90)
TIV	0.92 (0.37-2.33)	0.96 (0.001-11940)
NIV_IPI	**2.21 (1.50-3.38)**	2.16 (0.05-52.46)
DIC	6.17	7.53

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab. Bold type font indicates significant values.

Appendix Table 2: For advanced/metastatic RCC of intermediate-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
PLA	**2.00 (1.28-3.15)**	2.00 (0.01-1366)
IFN	**2.57 (1.86-3.57)**	2.56 (0.02-283)
SOR	0.96 (0.48-1.92)	0.95 (0.002- 5382)
PAZ	0.98 (0.80-1.20)	0.98 (0.02- 94.94)
AXI	0.80 (0.35-2.76)	0.80 (0.001- 7618)
EVE	**1.50 (1.11-2.03)**	1.50 (0.02-121.20)
CAB	0.64 (0.43-0.96)	0.65 (0.01- 64.02)
BEV_IFN	**1.68 (1.18-2.40)**	1.60 (0.01- 895.10)
TEM_BEV	**1.85 (1.21-2.81)**	1.81 (0.002- 4299)
TIV	0.77 (0.36-1.65)	0.79 (0.001- 15210)
NIV_IPI	**0.66 (0.54-0.81)**	0.67 (0.01- 64.51)
DIC	2.01	2.84

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab. Bold type font indicates significant values.

Appendix Table 3: For advanced/metastatic RCC of poor-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
IFN	1.88 (0.82- 4.42)	1.88 (0.03- 137.70)
EVE	1.70 (0.96- 3.01)	1.68 (0.02- 89.46)
CAB	0.75 (0.34-1.64)	0.75 (0.01- 54.64)
BEV_IFN	1.50 (0.60-3.74)	1.50 (0.01- 344.20)
TEM_BEV	1.21 (0.43-3.38)	1.22 (0.001- 1196)
NIV_IPI	**0.57 (0.44-0.76)**	0.57 (0.01- 36.17)
DIC	6.71	8.18

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon-α. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. Bold type font indicates significant values.

Appendix Table 4: Comparison of odds ratios (95% CI) for **high-grade adverse event** from consistency and inconsistency models.

Treatment compared with SUN	Consistency Model	Inconsistency Model
PLA	0.38 (0.02, 8.57)	0.39 (0.02, 7.99)
SOR	2.64 (0.06, 155.18)	2.83 (0.06, 150.54)
PAZ	1.02 (0.13, 9.41)	1.06 (0.12, 9.30)
TIV	1.84 (0.02, 177.32)	1.96 (0.02, 182.94)
CAB	0.91 (0.10, 8.90)	0.94 (0.11, 8.34)
SOR_IL-2	4.75 (0.06, 517.51)	5.05 (0.05, 509.65)
NIV_IPI	0.49 (0.06, 4.59)	0.50 (0.06, 4.18)
Random Effects Standard Deviation	0.83 (0.01, 1.69)	0.83 (0.06, 1.70)
Inconsistency Standard Deviation	NA	0.87 (0.04, 1.70)

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI = nivolumab plus ipilimumab.Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

Appendix Table 5: Comparison of odds ratios (95% CI) for **overall-grade adverse event** from consistency and inconsistency models.

Treatment compared with SUN	Consistency Model	Inconsistency Model
PAZ	2.26 (0.26, 25.07)	2.22 (0.27, 24.99)
CAB	1.10 (0.02, 34.61)	1.08 (0.02, 41.16)
NIV_IPI	0.34 (0.08, 1.38)	0.34 (0.08, 1.41)
Random Effects Standard Deviation	0.50 (0.02, 1.02)	0.53 (0.04, 1.02)
Inconsistency Standard Deviation	NA	0.53 (0.02, 1.03)

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab. Stepwise comparison of treatments did not find significant differences in rates of overall-grade adverse events.

Appendix Table 6: Comparison of results from primary analysis and sensitivity analysis for trials assessing approved targeted drugs.

Treatment	Primary Analysis PFS HR (95% CI) vs SUN	Sensitivity Analysis PFS HR (95% CI) vs SUN
PLA	**2.63 (1.47-4.71)**	**2.55 (1.38 -4.66)**
IFN	**2.70 (1.59-4.51)**	**2.71 (1.55 -4.71)**
SOR	1.47 (0.61-3.59)	1.48 (0.62 -3.55)
PAZ	1.03 (0.74-1.44)	1.02 (0.75 -1.41)
AXI	0.98 (0.36-2.76)	0.95 (0.35 -2.54)
EVE	1.21 (0.81-1.86)	1.20 (0.80-1.80)
BEV_IFN	1.66 (0.94 -2.88)	1.67 (0.92 -3.07)
TEM_BEV	**1.96 (1.04 -3.63)**	**2.00 (1.01 -4.03)**
TIV	0.92 (0.37-2.33)	**NA**
NIV_IPI	**2.21 (1.50-3.38)**	**2.18 (1.46-3.20)**

HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab. Bold type font indicates significant values.

BMJ Open

What's the optimum systemic treatment for advanced/metastatic renal cell carcinoma of favorable-, intermediate- and poor-risk, respectively? A systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034626.R1
Article Type:	Original research
Date Submitted by the Author:	22-Feb-2020
Complete List of Authors:	Cao, Guanghui; Henan Provincial People's Hospital Wu, Xiaoqiang; Henan Provincial People's Hospital Wang, Zhiwei; Henan Provincial People's Hospital Tian, Xiangyong; Henan Provincial People's Hospital Zhang, Chan; Henan Provincial People's Hospital, Department of Urology Wu, Xuan; Henan Provincial People's Hospital Zhang, Haotian; Henan Provincial People's Hospital Jing, Gaopeng; Henan Provincial People's Hospital Yan, Tianzhong; Henan Provincial People's Hospital,
Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology
Keywords:	Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY, IMMUNOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

What's the optimum systemic treatment for advanced/metastatic renal cell carcinoma of favorable-, intermediate- and poor-risk, respectively? A systematic review and network meta-analysis

Guanghui Cao, Xiaoqiang Wu, Zhiwei Wang, Xiangyong Tian, Chan Zhang, Xuan Wu, Haotian Zhang, Gaopeng Jing, Tianzhong Yan

Department of Urology, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Zhengzhou 450003, China;

[#] Correspondence to Prof Tianzhong Yan PhD, Department of Urology, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Zhengzhou 450003, China.

E-mail address: ytz460@hotmail.com (Tianzhong Yan), wuxiaoqiang2005@126.com (Xiaoqiang Wu).

Tel.: + 86 731 87160355; fax: + 86 431 87160356.

Abstract

Purpose: The optimum systemic therapies for advanced/metastatic renal cell carcinoma (RCC) of favorable-, intermediate-, and poor-risk have not been established. We aimed to compare and rank the effects associated with systemic therapies in the first-line setting.

Methods: We searched Pubmed, Cochrane databases, Web of Science, and ClinicalTrials.gov for randomized controlled trials (RCTs) published up to February 2020, of all available treatments for advanced/metastatic RCC. Analysis was done on a Bayesian framework.

Results: 15 unique RCTs including 8 995 patients were identified. For advanced/metastatic RCC of favorable-risk, avelumab plus axitinib was associated with a significantly higher improvement in progression-free survival (PFS) than sunitinib (HR 0.57, 95% CI 0.34-0.96). For intermediate-risk patients, cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.63, 95% CI 0.44-0.97; HR 0.66, 95% CI 0.53-0.81; HR 0.58, 95% CI 0.44-0.80; HR 0.62, 95% CI 0.47-0.83, respectively); pembrolizumab plus axitinib and nivolumab plus ipilimumab were associated with significantly higher improvement in overall survival (OS) than sunitinib (HR 0.53, 95% CI 0.34-0.81; HR 0.66, 95%CI 0.50-0.87, respectively). For poor-risk patients, nivolumab plus ipilimumab and pembrolizumab plus axitinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.43-0.76; HR 0.48, 95% CI 0.30-0.82, respectively); nivolumab plus ipilimumab and pembrolizumab plus axitinib were significantly more efficacious for OS than sunitinib (HR 0.57, 95% CI 0.39-0.883; HR 0.43, 95% CI 0.23-0.80, respectively). For OS, there were 81% and 78% probabilities that pembrolizumab plus axitinib was the best option for intermediate-risk and poor-risk patients, respectively.

Conclusion: Avelumab plus axitinib might be the optimum treatment for advanced/metastatic RCC of favorable-risk. Pembrolizumab plus axitinib might be the optimum treatment for intermediate-risk and poor-risk patients.

Keywords: renal cell carcinoma; systemic therapies; risk stratification; efficacy; safety.

Strengths and limitations of this study

► This is the first network analysis to compare systemic treatments for advanced/metastatic RCC separately by risk groups.

► Various statistical models were applied to synthesize data. The reliability and accuracy of results were corroborated by the low statistical heterogeneity and excellent model fit.

►Assessment of both efficacy and adverse events provides new insights into the benefit-harm balance of different systemic treatments.

►Main limitation lies in the reporting quality of trials included.

1. Introduction

Renal cell carcinoma (RCC) comprises approximately 90% of renal cancer, and represents approximately 2-3% of all new cancers worldwide [1]. It was estimated that there would be 62 700 new cases of renal cancer and 14 240 renal cancer-related deaths in the United States in 2016 [2]. In the European Union, new renal cancer cases and deaths in 2012 were approximately 84 400 and 34 700, respectively [3]. Up to 30% of patients were presented with advanced /metastatic RCC at the time of initial diagnosis [4 5]. Advanced/metastatic RCC is not a single condition, but is actually a heterogeneous group of conditions with different prognosis. The most widely accepted prognostic model is from the Memorial Sloan Kettering Cancer Center (MSKCC) and stratifies patients into favorable-, intermediate-, and poor-risk groups depending on the existence of well-characterized laboratory and clinical risk factors. The 2-year survival rates were 45%, 17%, and 3% for favorable-, intermediate-, and poor-risk groups, respectively [6]. In this systematic review, we focus on favorable-, intermediate-, and poor-risk patients with advanced/metastatic RCC.

In recent years, systemic treatment for advanced/metastatic RCC has changed from cytokines to drugs targeting angiogenesis. In 2007, results from two RCTs have been published reporting progress-free survival improvement of two newer targeted agents (sunitinib and sorafenib)[7 8]. To date, eight targeted drugs have been approved for treating advanced/metastatic RCC both in USA and Europe: five tyrosine kinase inhibitors (TKIs): sunitinib, sorafenib, pazopanib, cabozantinib, and axitinib; two mammalian target of rapamycin (mTOR) complex 1 kinase inhibitors: temsirolimus, and everolimus; and the recombinant humanized antivascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab combined with interferon-α (IFN-α). All eight targeted drugs showed significant survival benefit in randomized trials and established a prominent role in treating advanced/metastatic RCC [7 9-15]. More recently, immune checkpoint antibodies have introduced a new treatment option. CheckMate 214 reported that nivolumab plus ipilimumab was associated with a significantly higher overall survival than sunitinib in the first-line setting [16]. To further improve their efficacy, the combination of different classes of agents is

currently evaluated in clinical trials [17-20]. However, there are insufficient head-to-head RCTs to directly investigate the comparative effectiveness of all available therapies. Given the variety of treatment options for patients advanced/metastatic RCC and the limited evidence regarding the optimum treatment strategy, it is a challenge for clinicians to make the best decision.

In the present study, we performed a Bayesian network meta-analysis to compare first-line systemic treatments for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively. Network meta-analysis enables indirect comparisons based on a common comparator treatment when a head-to-head trial is unavailable and integrates direct and indirect comparisons to compare several treatment strategies while fully respecting randomization [21 22]. We aimed to summarize and compare the efficacy and safety associated with currently available systemic therapies for treating advanced/metastatic RCC of different risk categories using network meta-analysis.

2. Methods

2.1. Literature-search strategy

A comprehensive literature search was performed in Pubmed, Web of Science, ClinicalTrials.gov, and Cochrane databases for RCTs of systemic therapies of advanced/metastatic RCC (appendix for all search terms). All the reference lists of identified trials and related reviews were examined to find potential trials. The search was conducted in February 2020. There were no publication date or language restrictions.

2.2. Inclusion and exclusion criteria

All studies were selected according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria [23]. Studies were included if they satisfied three criteria: (1) the study enrolled patients who had histologically or cytologically confirmed advanced/metastatic RCC of favorable-, intermediate-, or poor-risk; (2) patients were randomly assigned to receive systemic

therapies alone or in combination. Relevant interventions included, but were not restricted to: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab, ipilimumab, axitinib, tivozanib, everolimus, temsirolimus, or bevacizumab plus IFN-α. Previous systemic therapy for advanced/metastatic RCC was not allowed; (3) one or more of the outcomes of interest mentioned below were reported. Nonoriginal articles, duplicate reports and non-RCTs were excluded.

2.3. Data Extraction and Quality Assessment

Two researchers (GH. Cao and XQ. Wu) examined the manuscripts of included trials independently, and extracted data into a structured form, including patient characteristics, treatment strategies, and interest outcomes [progress free survival (PFS), overall survival (OS), high-grade (grade ≥ 3) and overall drug-related adverse events]. We gave priority to extracting data from intention-to-treat analyses. The methodological quality of included RCTs was assessed using the Cochrane risk of bias assessment tool [24]. Disagreement between investigators was resolved by consensus.

2.4. Data synthesis and analysis

First, we performed traditional meta-analyses to compare the treatments using Stata v.12 (StataCorp, College Station, TX, USA). We applied the chi-square test and the I^2 statistic to investigate the possibility of heterogeneity among studies. A P value < 0.10 or an I2 > 50% suggested the presence of substantial heterogeneity.

Second, we did Bayesian network meta-analyses. For meta-analysis of PFS and OS, the reported adjusted hazard ratios (HRs) with 95% CIs were applied as the outcome measure. For studies not reporting HRs, we calculated them from Kaplan-Meier curve and information on follow-up with the pragmatic approach reported by Tierney et al [25]. For drug-related adverse events, we calculated odds ratios (ORs) using the available raw data abstracted from the trials. Both random-effects and fixed-effects models were performed for the analyses [26]. Goodness of model fit was assessed using the deviance information criterion and between-study standard deviation [26

27]. Convergence was determined graphically according to the method described by Gelman *et al* [28].

It is believed that certain systemic treatments are effective in certain risk groups than others, for example sunitinib is more effective in favorable-risk patients and nivolumab plus ipilimumab is more effective in intermediate and poor-risk patients [29], suggesting that there is a treatment-by-risk group (favorable-, intermediate-, and poor-risk groups) interaction. Taking no account of this possible interaction in the analysis, transitivity assumption across all included trials would be violated. Therefore, we performed all network analyses separately by risk groups (favorable-, intermediate-, and poor-risk groups) according to the MSKCC or IMDC risk model to assure transitivity assumption.

One key assumption for network analysis is that direct and indirect comparisons do not disagree beyond chance [26 30]. To explore for evidence of inconsistency in the network, investigators compared the estimated treatment effects from the entire network with traditional pair-wise estimates [30]. Sensitivity analyses were performed restricted to trials that assessed approved systemic therapies (sunitinib, sorafenib, pazopanib, cabozantinib, axitinib, everolimus, temsirolimus, bevacizumab plus IFN-α, and nivolumab plus ipilimumab). Publication bias and small-study effects were assessed using funnel plots [31].

We performed the Bayesian network analysis using OpenBUGS version 3.2.2 for PFS, and Gemtc version 0.14.3 (van Valkenhoef *et al*, 2012) for adverse events. For PFS, we applied 15 000 iterations obtained after a training phase of 10 000-iteration. In order to minimize autocorrelation, we applied a thinning interval of 50 for each chain. For adverse events, we applied the 60 000 iterations after a training phase of 40 000 iterations. The treatments were ranked in terms of PFS, OS, and high-grade AEs, respectively, using the surface under the cumulative ranking curve (SUCRA) and the distribution of the ranking probabilities [32].

3. Results

3.1. Search results and study characteristics

The literature search yielded 2 017 potentially eligible studies, of which 1 873 were excluded based on screening titles and abstracts (Fig. 1). The full text of 144 remaining studies were analyzed, and finally 21 publications reporting 15 unique RCTs were included (Table), involving 8 995 participants randomly assigned to one of the 13 treatment strategies: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab plus ipilimumab, axitinib, tivozanib, everolimus, IFN-α, bevacizumab plus IFN-α, temsirolimus plus bevacizumab, avelumab plus axitinib, and pembrolizumab and axitinib. According to the MSKCC or IMDC criteria, there were 2 783, 5 474 and 721 participants had favorable-, intermediate-, and poor-risk disease, respectively.

The main characteristics of included RCTs are summarized in Table. The demographic characteristics of patients were well balanced across trials. Enrolled patients across trials were similar in terms of age, gender, and risk classification. Across trials, the median age of patients ranged from 58 to 64 years. The participants were predominantly male (71.7%, 6 451 of 8 995). The included trials were designed similarly. Median follow-up ranged from 10.7 to 58 months. The mean sample sizes were 100, 192 and 32 patients per group for favorable-, intermediate- and poor-risk subtypes, respectively. Thirteen trials selected for clear-cell carcinoma subtypes [10-12 15 16 33-40], and two trials also included small subsets of non-clear-cell histotypes, each comprising 11% and 14% of the study population, respectively [41 42]. All studies were two-arm trials. The dosages used in most of trials were within the recommended dose ranges.

In this network meta-analysis, results are reported based on fixed-effects models because they demonstrated better goodness of fit compared with random-effects models. The results of random-effects models are available in appendix Table 1-5.

3.2. Progression-free survival

3.2.1. For advanced/metastatic RCC of favorable-risk, 13 trials enrolling 2 514 total

patients reported adequate information on progression-free survival and contributed to network meta-analysis (Fig. 2A)[10-13 15 16 34-37 39-42]. Fig. 2B summarizes the results of the network meta-analysis for PFS. Compared with sunitinib, IFN-α and nivolumab plus ipilimumab were associated with significantly worse PFS (HR 2.69, 95% CI 1.54-4.67; and HR 2.18, 95% CI 1.47-3.25, respectively). Network meta-analysis showed that only avelumab plus axitinib was associated with a significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.34-0.96). Based on the results of ranking, there was a 45% chance that avelumab plus axitinib provided the greatest PFS benefit for patients with favorable-risk disease (SUCRA = 92.3%)(Fig. 2C).

3.2.2. For advanced/metastatic RCC of intermediate-risk, 14 trials enrolling 5 473 total patients contributed to the analysis of PFS (Fig. 3A) [10-13 15 16 33-37 39 40 42]. Network meta-analysis demonstrated that cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.63, 95% CI 0.44-0.97; HR 0.66, 95% CI 0.53-0.81; HR 0.58, 95% CI 0.44-0.80; HR 0.62, 95% CI 0.47-0.83, respectively). Everolimus, bevacizumab plus IFN-α, and temsirolimus plus bevacizumab were significantly less efficacious for PFS than sunitinib (HR 1.50, 95% CI 1.11-2.01; HR 1.69, 95% CI 1.18-2.41; HR 1.88, 95% CI 1.22-2.81, respectively) (Fig. 3B). Based on the analysis of ranking, pembrolizumab plus axitinib had the highest probability (49%) to be the best treatment for intermediate-risk patients (SUCRA = 90.7%). Avelumab plus axitinib and cabozantinib had a similar likelihood of being the second-best option for patients with intermediate-risk disease (Fig. 3C).

3.2.3. Based on data that was available for advanced/metastatic RCC of poor-risk, the network involved seven trials comparing nine different treatments (721 total patients; Fig. 4A) [15 16 33-35 37 39 40 42]. Network meta-analysis demonstrated that nivolumab plus ipilimumab and pembrolizumab plus axitinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.43-0.76;

HR 0.48, 95% CI 0.30-0.82, respectively) (Fig. 4B). On the base of ranking analysis, there was a 60% probability that pembrolizumab plus axitinib had the greatest PFS for poor-risk patients (SUCRA = 91.3%) (Fig. 4C).

3.3. Overall survival

Five RCTs reported OS according to risk subgroups, and data from three of them contributed to the network meta-analysis (572, 1801, and 407 patients for favorable-, intermediate-, and poor-risk, respectively)[16 38 39]. For advanced/metastatic RCC of favorable-risk, there is no significant OS benefit between sunitinib and pazopanib (HR 0.88, 95% CI 0.64-1.21) or pembrolizumab plus axitinib (HR 0.64, 95% CI 0.24-1.70) (Fig. 5A). For intermediate-risk patients, pembrolizumab plus axitinib and nivolumab plus ipilimumab were associated with significantly higher improvement in OS than sunitinib (HR 0.53, 95% CI 0.34-0.81; HR 0.66, 95% CI 0.50-0.87, respectively)(Fig. 5B). For advanced/metastatic RCC of poor-risk, pembrolizumab plus axitinib and nivolumab plus ipilimumab were significantly more efficacious for OS than sunitinib (HR 0.43, 95% CI 0.23-0.80; HR 0.57, 95% CI 0.39-0.83, respectively) (Fig. 5C). Based on the results of ranking, there were 81% and 78% probabilities for pembrolizumab plus axitinib to be the best choice for intermediate- and poor-risk patients, respectively (SUCRA =93.1% ; SUCRA= 91.4%, respectively) (appendix Fig.1-3).

3.4. Adverse events

Nine trials contributed to our analysis of overall and high-grade drug-related adverse events [10 11 13 15 16 36 39-41]. All the nine trials did not provide adverse events data for different risk groups, so we extracted a summary of adverse event data. Results of comparisons of adverse events of nine systemic treatments are presented in Fig. 6 and appendix Fig. 4 Stepwise comparison of all the seven therapies did not find significant differences in rates of high-grade or overall adverse events. The most common adverse events included diarrhea, hypertension, fatigue, and decreased appetite.

3.5. Network assumptions, sensitivity analysis, publication bias, and risk of bias

Consistencies between direct and indirect evidence were noted for any comparisons (appendix Fig. 5 and appendix Table 1-5). Results from the sensitivity analyses were in line with the primary analysis (appendix Table 6).The comparison-adjusted funnel plot (Fig. 7) for PFS was largely symmetric, indicating no obvious small-study effects and publication bias. The methodological quality was moderate in the included studies (appendix Fig. 6). All trials were thought to have low risk of bias for random sequence generation, incomplete outcome data, and selective reporting of outcomes. Ten trials had evidence of high risk of bias for masking [12 13 15 35-37 39-42].

4. Discussion

Our network meta-analysis of 15 RCTs including 8 995 individuals assessed the efficacy and safety of all major systematic therapies for the treatment of advanced/metastatic RCC in the first-line setting. Findings of this meta-analysis might help to choose among systemic agents for the management of patients with previously untreated advanced/metastatic RCC. In terms of PFS, avelumab plus axitinib was most likely to be the best treatment regimen for advanced/metastatic RCC of favorable-risk, and pembrolizumab plus axitinib seemed to be the most efficacious treatment strategy for patients with intermediate- and poor-risk. In terms of OS, there were no significant differences among systematic therapies for advanced/metastatic RCC of favorable-risk, and pembrolizumab plus axitinib was probably to be the best option for patients with intermediate- and poor-risk. In terms of drug-related adverse events, there were no significant differences among systemic therapies.

In RCC with clear cell subtype, hypoxia-inducible factor (HIF) accumulation due to loss of von Hippel-Lindau (VHL) leads to overexpression of VEGF and platelet derived growth factor (PDGF), which promotes tumor angiogenesis [43 44]. This process substantially makes a contribution to the development and progression of clear cell RCC. Inhibiting the VEGF signaling has been supposed as the key mechanism for antitumor effects in clear cell RCC. To date, eight targeted drugs have

been approved for treating advanced RCC: sunitinib, sorafenib, pazopanib, cabozantinib, axitinib, everolimus, temsirolimus, and bevacizumab (in combination with IFN-α).

As shown in this analysis, for patients with intermediate-risk, sunitinib resulted in a significant PFS benefit compared with everolimus. The varied clinical benefit could be associated with mechanisms of action of TKI and mTOR inhibitor. Sunitinib not only inhibit VEGF receptors -1, -2, and -3, which may be the most clearly relevant targets in RCC so far, but also exhibit potent activity against PDGF receptor[11 45]. It has been reported that PDGF plays a critical role in the recruitment of pericytes to sprouting tumor vessels, and pericyte-covered vessels are more likely resistant to anti-vascular therapy than those pericyte-negative vessels [46 47]. The mTOR complex is the upstream of an intracellular signaling network regulating cell growth and angiogenesis, and it plays a key role in the pathogenesis of advanced/metastatic RCC [48]. It has been demonstrated that rapamycin analogs, including everolimus and temsirolimus, inhibit only one of two signaling complexes of mTOR [49]. The mTORC1 signaling is potently inhibited by everolimus and temsirolimus, while the mTORC2 signaling is not [50]. Consequently, one downstream signaling of mTOR activation is unopposed. The relatively unsatisfactory efficacy should disable the mTOR inhibitors as more suitable therapies for the treatment of advanced/metastatic RCC than TKIs. Regarding TKIs, our results suggest that sunitinib was most likely to be the best treatment regimen for patients with favorable-risk disease.

A potentially additive benefit from combinations of targeted drugs has been suggested on the basis that they inhibit separate cellular pathways. However, our results show that temsirolimus plus bevacizumab, and bevacizumab plus IFN-α provide little survival benefit compared with sunitinib, further confirming absence of evidence that combination treatment simultaneously inhibiting both VEGF and mTOR signaling results in therapeutic synergy [18 20 37].

Immune checkpoint antibodies block the inhibitory T-cell receptor programmed death-1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4)-signaling to augment tumor specific immune response [51]. Nivolumab (an anti-PD-1 antibody) is

approved for the treatment of advanced RCC in the second line setting. Ipilimumab (an anti- CTLA-4 antibody) is approved for the treatment of advanced melanoma. Nivolumab plus ipilimumab has been reported significant efficacy in multiple tumor types [52 53]. In this analysis, pembrolizumab plus axitinib appeared to be the optimum treatment for intermediate- and poor-risk patients. Single-agent anti-tumor activity of pembrolizumab and axitinib for mRCC has been reported in previous studies [12 54]. Accordingly, axitinib in combination with pembrolizuma was assessed and contributed to objective response rate in 73% patients in a phase 1b trial [55]. Our result was in consistent with results of KEYNOTE-426 trial, demonstrating that pembrolizumab plus axitinib resulted in significant OS and PFS benefit compared with sunitinib [39]. In addition, the survival benefit of pembrolizumab plus axitinib was observed independent of PD-L1 status [39].

Pembrolizumab plus axitinib is a combination of anti- PD-1 monoclonal antibody and VEGF receptor TKI. Immune checkpoint inhibitors (ICI) block the inhibitory T-cell receptor PD-1 or CTLA-4-signaling to augment tumor specific immune response [51]. Besides of antiangiogenic effects, VEGF inhibition could enhance the recruitment and infiltration of immune cells into the tumors [56 57]. It's reported that simultaneous blockade of PD-1 and VEGF receptor-2 induced decreased tumor neovascularization and tumor inhibition in a murine model [58]. These studies suggested that the combination of ICI and VEGF receptor inhibitors could provide enhanced benefit for mRCC. Recently, in addition to pembrolizumab plus axitinib, avelumab (anti-PD-L1 antibody) plus axitinib, and atezolizumab (anti-PD-L1 antibody) plus bevacizumab were respectively assessed in two phase 3 RCTs (IMmotion 151 and JAVELIN Renal 101), and both of them showed significant survival benefit for mRCC compared with sunitinib [39 59].However, there is no head-to-head trial comparing combinations of ICI and VEGF receptor inhibitors inhibitors (pembrolizumab plus axitinib, aveluma plus axitinib, and atezolizumab plus bevacizumab) directly. In consistent with our previous study, the present analysis revealed that pembrolizumab plus axitinib presented the highest OS benefit for intermediate- and poor-risk patients. For advanced/metastatic RCC of favorable-risk,

only avelumab plus axitinib was associated with a significantly higher improvement in PFS than sunitinib, suggesting avelumab plus axitinib might be the optimum treatment for favorable-risk patients. Considering patients continued to be followed for OS in the JAVELIN Renal 101 trial [40], the real OS benefit for avelumab plus axitinib over sunitinib requires additional follow-up.

Recently, several network meta-analyses were attempted to investigate the comparative effects of different systemic agents for treatment of advanced/metastatic RCC [60-63]. However, trials included in the meta-analyses enrolled patients with different risk groups. The analysis used aggregate data and did not perform subgroup analysis based on risk strata. In the present study, we performed a network meta-analysis to compare first-line systemic treatments for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively， thus providing physicians with the optimal treatment for different risk groups.

The strengths of our study are as follows. To the best of our knowledge, this study is the first network analysis to compare systemic treatments for advanced/metastatic RCC separately by risk groups. We applied multiple rigorous search strategies to retrieve all potentially eligible RCTs. In the present study, we comprehensively compared and ranked all available first-line systemic therapies for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively, thus providing physicians with an overall appraisal of systemic therapies for different risk groups. In addition, we used Bayesian network meta-analysis to synthesize data. This approach provides indirect effect estimates in the absence of head-to-head trial and incorporates all available information from RCTs while fully maintaining randomization [21 22]. We applied various statistical models to increase reliability of the results. Results were consistent across all analyzed outcomes. Moreover, the reliability and accuracy of results were corroborated by the low statistical heterogeneity and excellent model fit. Finally, assessment of both efficacy and adverse events provides new insights into the benefit-harm balance of different systemic treatments.

However, the limitations of our study must be taken into account. The major

limitation of this network meta-analysis lies in the reporting quality of trials reviewed. Ten included trials were not masked, which might affect the validity of our findings. In addition, three included trials (CABOSUN, ROSORC, and RECORD-3) are phase 2 RCTs with smaller sample size, and they may be less authoritative compared with phase 3 RCTs. Moreover, most of the trials did not perform the analysis of OS in risk subgroupd, which made it impossible to assess the OS benefits of all the existing treatments for different risk patients. In addition, this meta-analysis was conducted based on summary statistics rather than individual patient level data. There might be some confounding factors (*e.g.*, ethnic origin, prior nephrectomy, *etc*.) at the individual patient level that might influence the benefit of systemic treatments, but were not available; therefore analyses adjusted for these factors were impossible in our network meta-analysis. Access to patient-level longitudinal data would allow us to establish more robust and accurate conclusions in specific subgroups of patients. Moreover, the length of follow-up varied across studies, resulting in potential variations in survival benefits and adverse events. Due to only eight trials reporting median follow-up, sensitivity analyses adjusted for this factor were impossible. Moreover, individual dosage varied across studies and data were too sparse to investigate effects of different schedules, which might somewhat affect the generalisability of our findings. Since the analysis was based on highly selected RCTs and the results were based on fixed-effects models, findings in this analysis may not be entirely generalized to real-world practice. Finally, findings in this meta-analysis were mainly based on patients with clear-cell advanced RCC, thus no robust recommendations can be provided for non-clear-cell subtypes. Two trials included small subsets of non-clear-cell histotypes (11% and 14% of the study population), which might somewhat damage the results of our analysis.

5. Conclusions

Our network meta-analysis suggested that: avelumab plus axitinib might be the optimum treatment for advanced/metastatic RCC of favorable-risk; pembrolizumab plus axitinib was most likely to be the best option for intermediate- and poor-risk

patients. Further well-designed, large-scale RCTs are required to confirm and update the findings of this analysis.

Author Contributions

G-HC and X-QW conceived and designed the meta-analysis, Z-ZW and X-YT identified and acquired reports of trials, and extracted data. XW and H-TZ analyzed and interpreted the data. CZ and G-PJ contacted authors of trials for additional information. G-HC and X-QW drafted the manuscript. T-ZY critically reviewed the manuscript. All authors approved the final submitted version of the report.

Fundings: This research was supported by the Henan Provincial Medical Scientific and Technological Research Project (Grant No. 201702191). The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflicts of Interest: None declared.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research.

References:

1. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67(5):913-24.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7-30.
3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374-403.
4. Janzen NK, Kim HL, Figlin RA, et al. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003;30(4):843-52.
5. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005;353(23):2477-90.
6. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies Against Advanced Renal Cell Carcinoma. Journal of Clinical Oncology 2002;20(1):289-96.
7. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356(2):115-24.
8. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356(2):125-34.
9. Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008;26(33):5422-8.
10. Negrier S, Jager E, Porta C, et al. Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. Med Oncol 2010;27(3):899-906.
11. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28(6):1061-8.
12. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol 2013;14(13):1287-94.
13. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369(8):722-31.
14. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27(8):1280-9.
15. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. Journal of Clinical Oncology 2017;35(6):591-97.
16. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378(14):1277-90.

17. Jonasch E, Corn P, Pagliaro LC, et al. Upfront, randomized, phase 2 trial of sorafenib versus sorafenib and low-dose interferon alfa in patients with advanced renal cell carcinoma: clinical and biomarker analysis. Cancer 2010;116(1):57-65.
18. Negrier S, Gravis G, Perol D, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol 2011;12(7):673-80.
19. Procopio G, Verzoni E, Bracarda S, et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: the ROSORC trial. Br J Cancer 2011;104(8):1256-61.
20. Ravaud A, Barrios CH, Alekseev B, et al. RECORD-2: phase II randomized study of everolimus and bevacizumab versus interferon alpha-2a and bevacizumab as first-line therapy in patients with metastatic renal cell carcinoma. Ann Oncol 2015;26(7):1378-84.
21. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331(7521):897-900.
22. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23(20):3105-24.
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of internal medicine 2009;151(4):W65-94
24. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343.
25. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
26. Dias S, Welton NJ, Sutton AJ, et al. A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. Medical Decision Making 2014.
27. Spiegelhalter DJ, Best NG, Carlin BP, et al. Bayesian measures of model complexity and fit. Journal of The Royal Statistical Society Series B-statistical Methodology 2002;64(4):583-639.
28. Gelman A, Rubin DB. Markov chain Monte Carlo methods in biostatistics. Stat Methods Med Res 1996;5(4):339-55.
29. Powles T, Albiges L, Staehler M, et al. Updated European Association of Urology Guidelines Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. Eur Urol 2017;73(3):311-15.
30. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making 2013;33(5):641-56.
31. Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8(10):e76654.
32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64(2):163-71.

33. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 2010;28(13):2144-50.
34. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol 2010;28(13):2137-43.
35. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27(22):3584-90.
36. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013;31(30):3791-9.
37. Rini BI, Bellmunt J, Clancy J, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. J Clin Oncol 2014;32(8):752-9.
38. Motzer RJ, Hutson TE, McCann L, et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. N Engl J Med 2014;370(18):1769-70.
39. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380(12):1116-27.
40. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380(12):1103-15.
41. Procopio G, Verzoni E, Bracarda S, et al. Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): final results of the ROSORC trial. Ann Oncol 2013;24(12):2967-71.
42. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32(25):2765-72.
43. Patard JJ, Rioux-Leclercq N, Fergelot P. Understanding the importance of smart drugs in renal cell carcinoma. Eur Urol 2006;49(4):633-43.
44. Costa LJ, Drabkin HA. Renal cell carcinoma: new developments in molecular biology and potential for targeted therapies. Oncologist 2007;12(12):1404-15.
45. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 2003;9(1):327-37.
46. Benjamin LE, Hemo I, Keshet E. A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF. Development 1998;125(9):1591-8.
47. Gee MS, Procopio WN, Makonnen S, et al. Tumor vessel development and maturation impose

limits on the effectiveness of anti-vascular therapy. Am J Pathol 2003;162(1):183-93.
48. Creighton CJ, Morgan M, Gunaratne PH, et al. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature 2013;499(7456):43-49.
49. Loewith R, Jacinto E, Wullschleger S, et al. Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. Mol Cell 2002;10(3):457-68.
50. Inoki K, Guan KL. Complexity of the TOR signaling network. Trends Cell Biol 2006;16(4):206-12.
51. Ribas A. Tumor immunotherapy directed at PD-1. N Engl J Med 2012;366(26):2517-9.
52. Hammers HJ, Plimack ER, Infante JR, et al. Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. J Clin Oncol 2017;35(34):3851-58.
53. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17(7):883-95.
54. McDermott DF, Lee J-L, Szczylik C, et al. Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (accRCC): Results from cohort A of KEYNOTE-427. Journal of Clinical Oncology 2018;36(15_suppl):4500-00.
55. Atkins MB, Plimack ER, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncol 2018;19(3):405-15.
56. Shrimali RK, Yu Z, Theoret MR, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010;70(15):6171-80.
57. Huang Y, Yuan J, Righi E, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proceedings of the National Academy of Sciences of the United States of America 2012;109(43):17561-6.
58. Yasuda S, Sho M, Yamato I, et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo. Clinical and experimental immunology 2013;172(3):500-6.
59. Rini BI, Powles T, Atkins MB, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet 2019;393(10189):2404-15.
60. Wallis CJD, Klaassen Z, Bhindi B, et al. First-line Systemic Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. Eur Urol 2018;74(3):309-21.
61. Wang J, Li X, Wu X, et al. Role of immune checkpoint inhibitor-based therapies for metastatic renal cell carcinoma in the first-line setting: A Bayesian network analysis. EBioMedicine 2019;47:78-88.
62. Hahn AW, Klaassen Z, Agarwal N, et al. First-line Treatment of Metastatic Renal Cell

Carcinoma: A Systematic Review and Network Meta-analysis. European urology oncology 2019;2(6):708-15.

63. Karner C, Kew K, Wakefield V, et al. Targeted therapies for previously treated advanced or metastatic renal cell carcinoma: systematic review and network meta-analysis. BMJ Open 2019;9(3):e024691.

Table: Studies included in the multiple-treatments meta-analysis

Study	Number of patients	Age (years) median(range)	Sex (% male)	MSKCC (%) Favorable	Intermediate	Poor	Median PFS in months (95% CI)	Hazard ratio (95% CI)
Motzer 2014 (RECORD-3)								
Everolimus	238	62 (20-89)	69.7	29	56	15	7.9	1.4 (1.2-1.8)
Sunitinib	238	62 (29-84)	73.9	30	56	14	10.7	1 (Ref)
Motzer 2014 (COMPARZ)								
Pazopanib	557	61 (18-88)	71	27	58	12	8.4 (8.3-10.9)	1.05 (0.90-1.22)
Sunitinib	553	62 (23-86)	75	27	59	9	9.5 (8.3-11.1)	1 (Ref)
Rini 2014 (INTORACT)								
Temsirolimus plus bevacizumab	400	59 (22-87)	72	28	65	8	9.1 (8.1-10.2)	1.1 (0.9-1.3)
Bevacizumab plus IFN-α	391	58 (23-81)	69	27	65	8	9.3 (9.0-11.2)	1 (Ref)
Procopio 2013 (ROSORC)								
Sorafenib plus interleukin-2	66	64 (57-69) *	79	55	41	5	NA	NA
Sorafenib	62	62 (52-69) *	69	55	39	6	NA	NA
Hudson 2013								
Axitinib	192	58 (23-83)	70	49	44	4	10.1 (7.2-12.1])	0.77 (0.56-1.05)
Sorafenib	96	58 (20-77)	77	55	42	2	6.5 (4.7-8.3)	1 (Ref)
Motzer 2013								
Tivozanib	260; treatment-naive 181	59 (23-83)	71	27	67	7	12.7 (9.1-15.0)	0.756 (0.580-0.985)
Sorafenib	257; treatment naive 181	59 (23-85)	74	34	62	4	9.1 (7.3-10.8)	1 (Ref)
Sternberg 2010 (VEG105192)								
Pazopanib	290; treatment naive 155	59 (28-82)	68	36	56	4	11.1	0.40 (0.27-0.60)
Placebo	n = 145; treatment naive 78	62 (25-81)	74	40	51	6	2.8	1 (Ref)
Motzer 2009								
Sunitinib	375	62 (27-87)	71	38	56	6	11 (11-13)	0.539 (0.451-0.643)
IFN-α	375	59 (34-85)	72	34	59	7	5 (4-6)	1 (Ref)
Negrier 2010 (TARGET)								
Sorafenib	451; treatment-naive 77	60	63.6	53.2	46.8	0	5.8	0.48 (0.32-0.73)
Placebo	452; treatment-naive 84	60.5	69	45.2	54.8	0	2.8	1 (Ref)
Rini 2010 (CALGB 90206)								
Bevacizumab plus IFN-α	369	61 (56-70)	73	26	64	10	8.5 (7.5-9.7)	0.71 (0.61-0.83)
IFN-α	363	62 (55-70)	66	26	64	10	5.2 (3.1-5.6)	1 (Ref)
Escudier 2010 (AVOREN)								
Bevacizumab plus IFN-α	327	61 (30–82)	68	27	56	9	10.2	0·61 (0·51-0·73)
IFN-α	322	60 (18–81)	73	29	56	8	5.4	1 (Ref)

Continued

Motzer 2018 (CheckMate 214)								
Nivolumab plus Ipilimumab	550	62 (26-85)	75	23	61	17	11.6 (8.7–15.5)	0.82(0.64-1.05)‡
Sunitinib	546	62 (21-85)	72	23	61	16	8.4 (7.0–10.8)	1 (Ref)
Choueiri 2017								
Cabozantinib	79	63 (40-82)	83.5	0	81.0§	19.0§	8.2 (6.2 to 8.8)	0.66 (0.46-0.95)
Sunitinib	78	64(31-87)	73.1	0	80.8§	19.2§	5.6 (3.4 to 8.1)	1 (Ref)
Motzer 2019 (JAVELIN Renal 101)								
Avelumab plus Axitinib	442	62 (29-83)	71.5	21.7	64.0	11.5	13.8 (11.1-NE)	0.69 (0.56-0.84)
Sunitinib	444	61 (27-88)	77.5	22.5	66.0	10.1	8.4 (6.9-11.1)	1 (Ref)
Rini 2019 (KEYNOTE-426)								
Pembrolizumab and Axitinib	432	62 (30-89)	71.3	31.9§	55.1§	13§	15.1 (12.6-17.7)	0.69 (0.57-0.84)
Sunitinib	429	61 (26-90)	74.6	30.5§	57.3§	12.1§	11.1 (8.7-12.5)	1 (Ref)

IFN-α = interferon-α; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; CI = confidence interval; AE = adverse event; NA=not available; Ref = reference group (hence hazard ratio set to 1);

* interquartile range; † mean; ǂ 99.1% CI; § IMDC risk group, International Metastatic Renal Cell Carcinoma Database Consortium

Legends for Figures

Fig. 1 - Literature search and selection

Fig. 2 - Analysis of progression-free survival for patients with favorable-risk disease.

(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of PFS, among the 13 treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

Fig. 3 - Analysis of progression-free survival for patients with intermediate-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

Fig. 4 - Analysis of progression-free survival for patients with poor-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon-α. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

Fig.5- Analysis of overall survival for patients with favorable- risk (A), intermediate- risk (B), and poor-risk (C). HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib.

Fig. 6 - Pooled odds ratios for high-grade adverse events.

The column treatment is compared with the row treatment. Odds ratios lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI

= nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib. Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis for hazard ratios of progression-free survival

SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

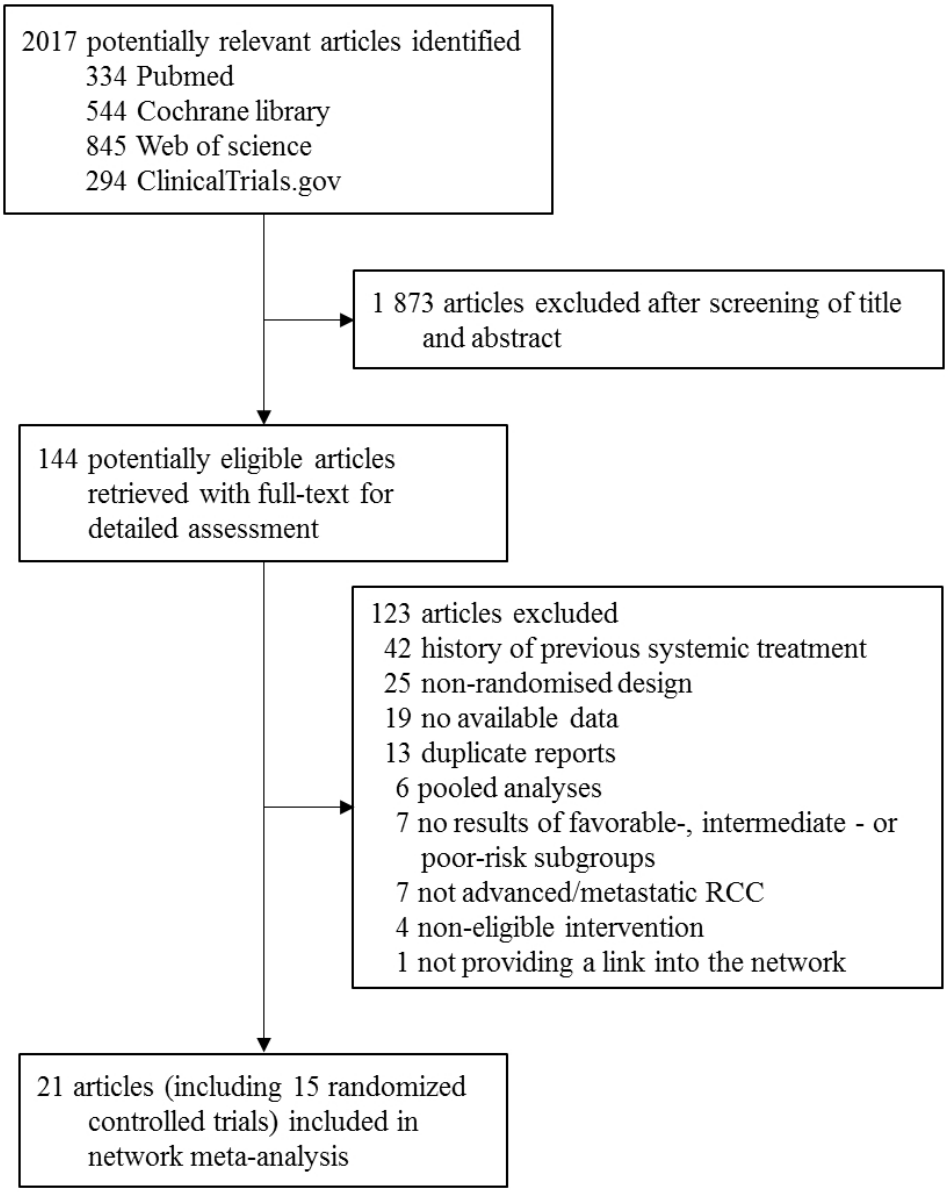


Fig. 1 - Literature search and selection

140x174mm (150 x 150 DPI)

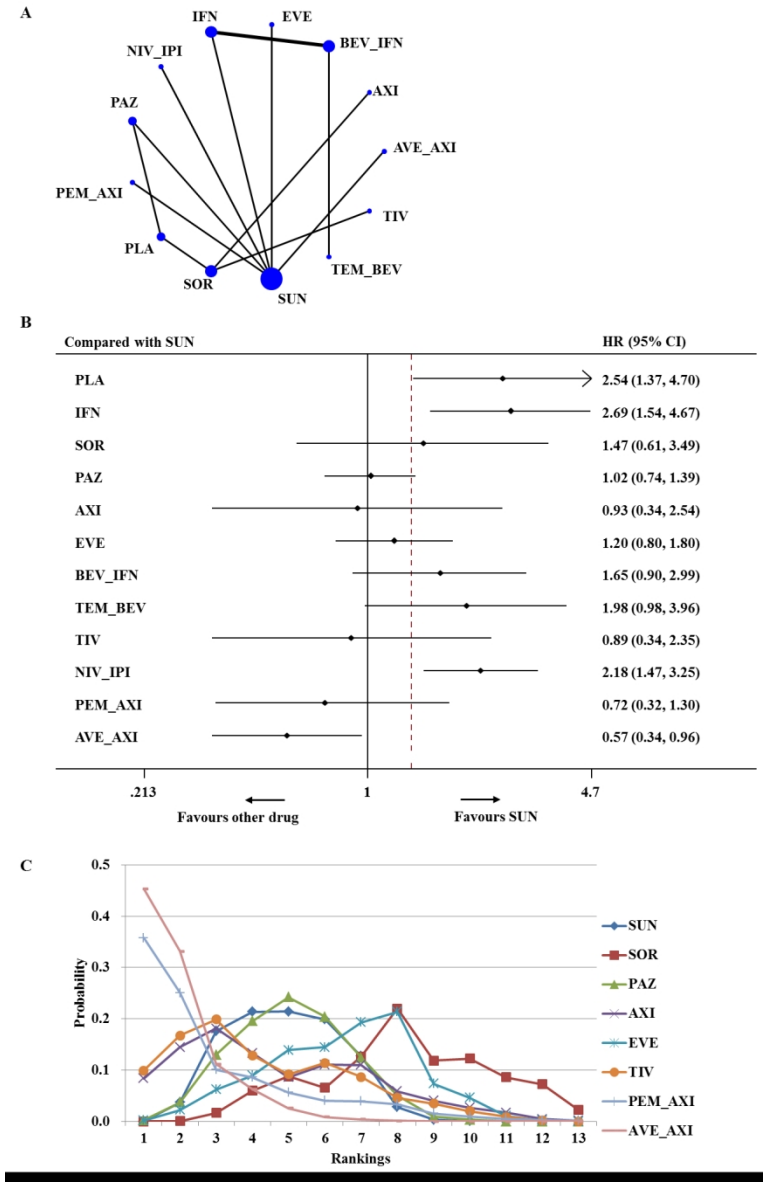


Fig. 2 - Analysis of progression-free survival for patients with favorable-risk disease.
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of PFS, among the 13 treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

220x347mm (150 x 150 DPI)

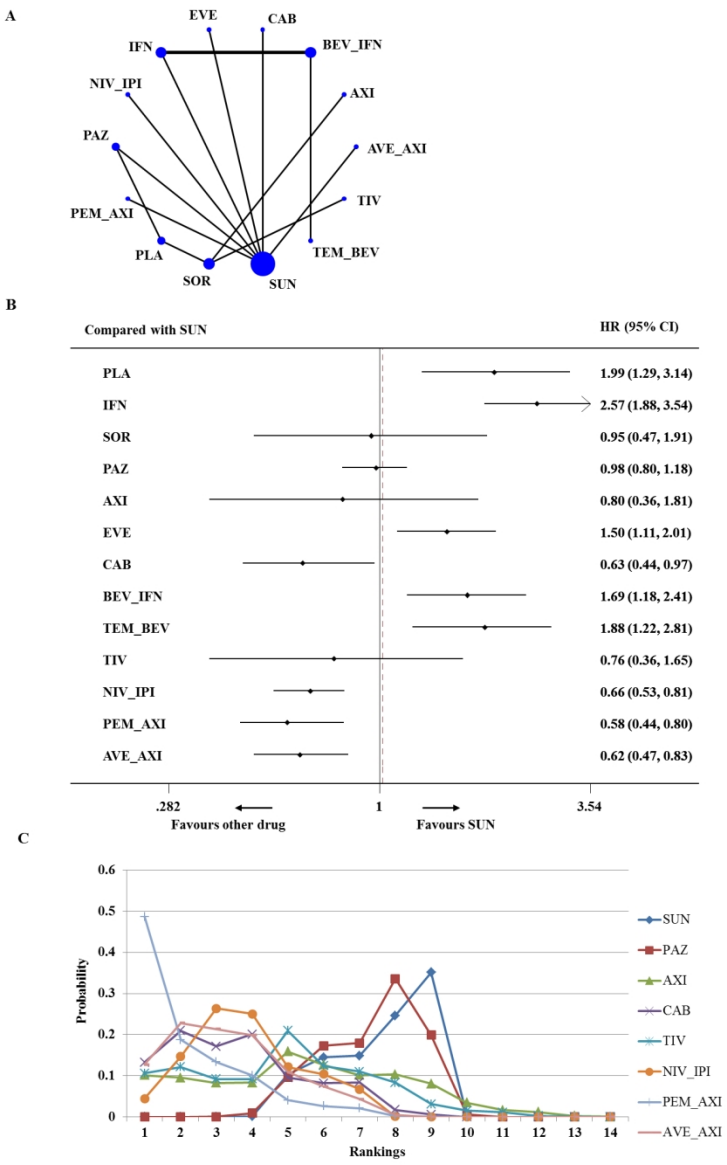


Fig. 3 - Analysis of progression-free survival for patients with intermediate-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

235x369mm (150 x 150 DPI)

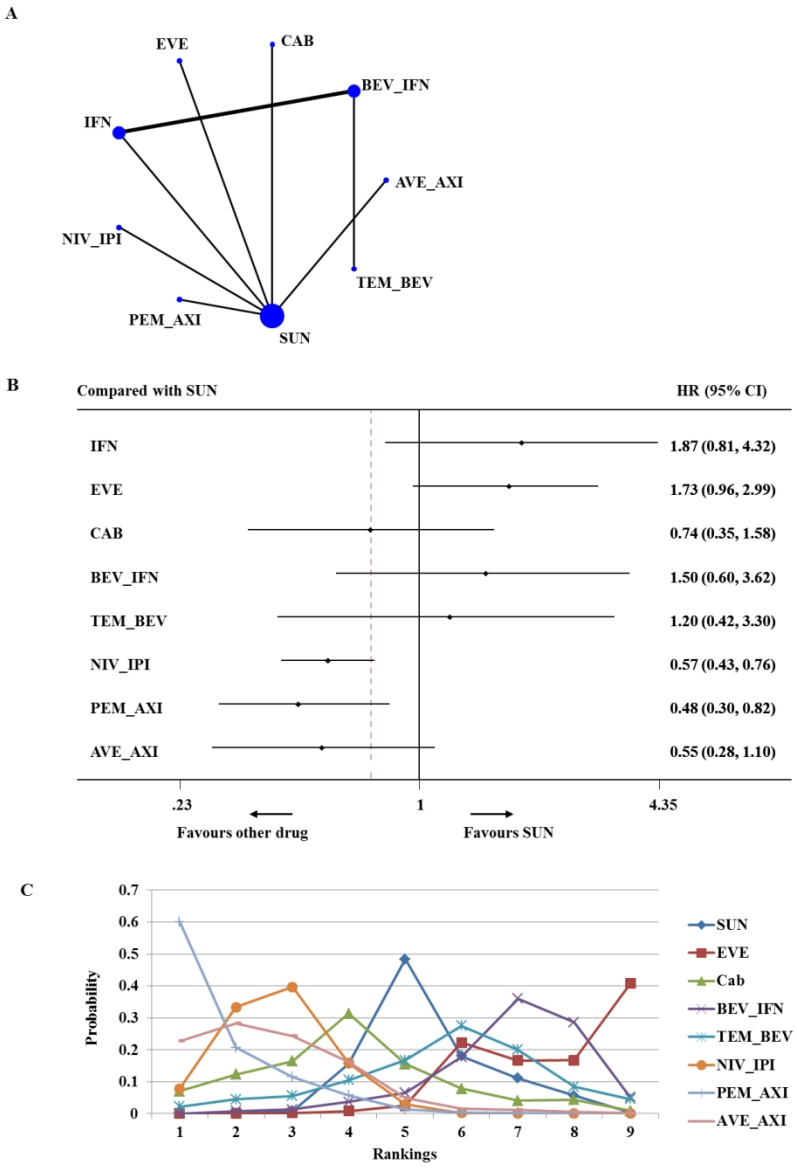


Fig. 4 - Analysis of progression-free survival for patients with poor-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon-α. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

221x322mm (150 x 150 DPI)

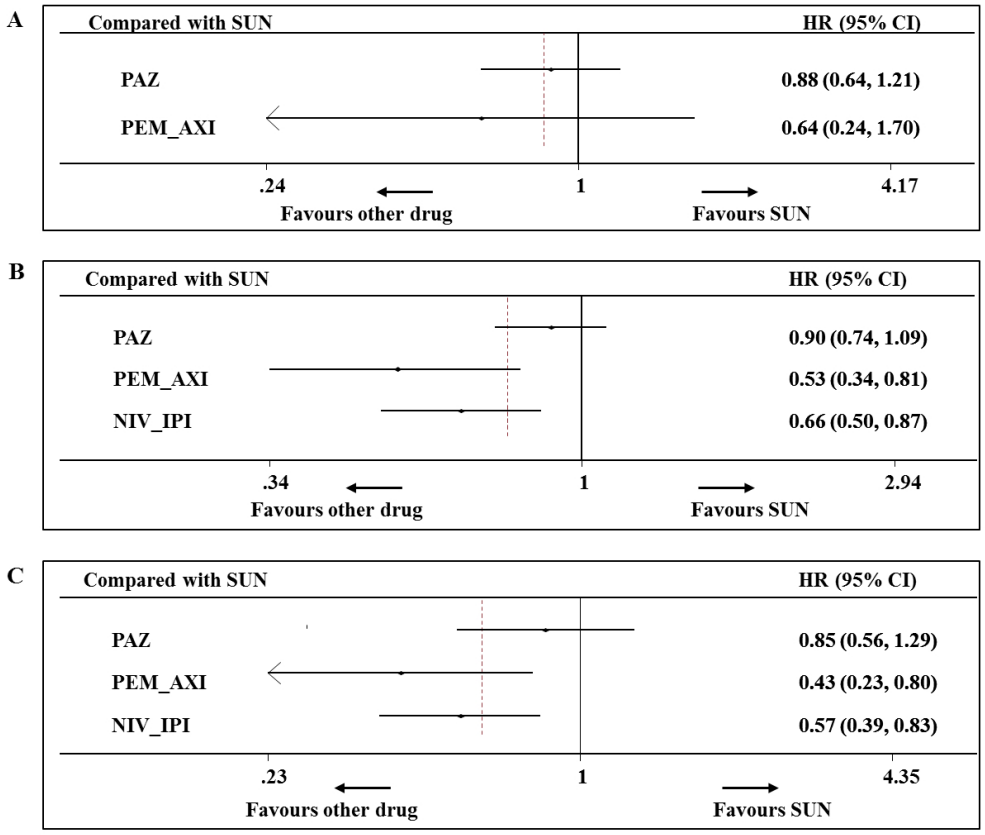


Fig.5- Analysis of overall survival for patients with favorable- risk (A), intermediate- risk (B), and poor-risk (C). HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib.

205x173mm (150 x 150 DPI)

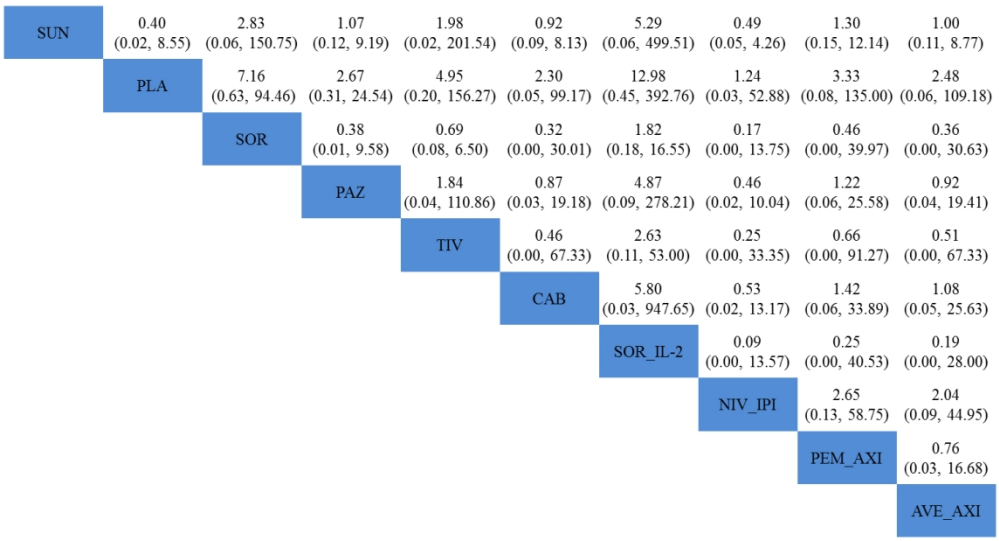


Fig. 6 - Pooled odds ratios for high-grade adverse events.
The column treatment is compared with the row treatment. Odds ratios lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib. Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

256x138mm (150 x 150 DPI)

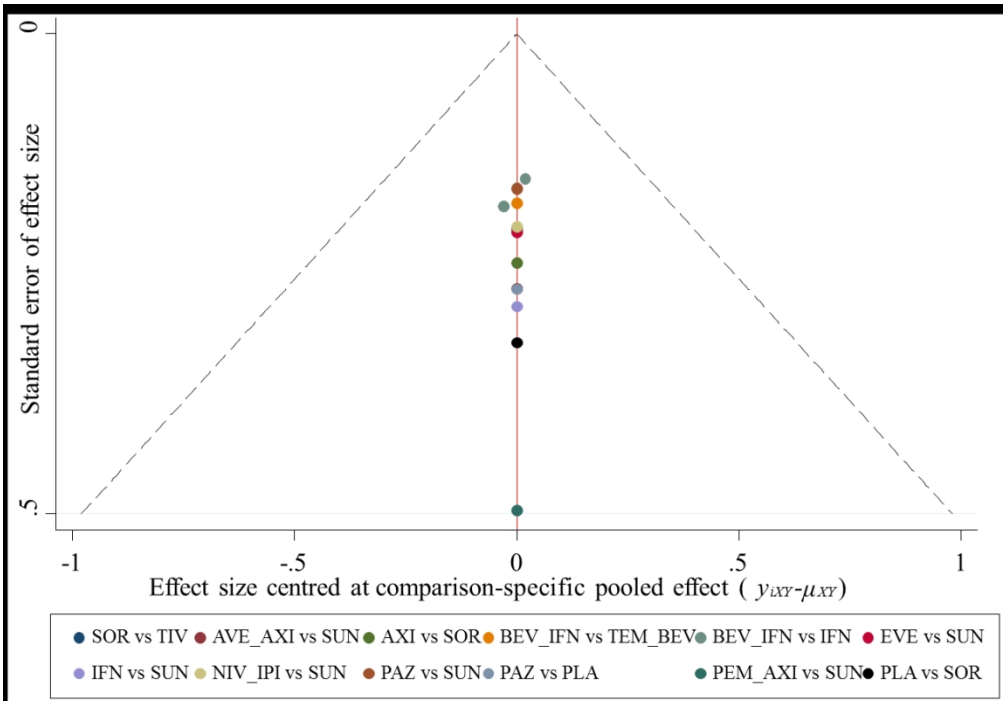


Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis for hazard ratios of progression-free survival

SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

215x150mm (150 x 150 DPI)

Appendix

Search strategy

Pubmed:

((((((((((((sorafenib[Title/Abstract]) OR sunitinib[Title/Abstract]) OR bevacizumab[Title/Abstract]) OR pazopanib[Title/Abstract]) OR temsirolimus[Title/Abstract]) OR everolimus[Title/Abstract]) OR axitinib[Title/Abstract]) OR Cabozantinib[Title/Abstract]) OR IFN-alpha[Title/Abstract]) OR IL-2[Title/Abstract]) OR Nivolumab[Title/Abstract]) OR Immune checkpoint blockade[Title/Abstract])) AND (("Carcinoma, Renal Cell"[Mesh]) OR ((((renal cancer[Title]) OR renal carcinoma[Title]) OR kidney cancer[Title]) OR kidney carcinoma[Title]))
Filter: Controlled Clinical Trial

Cochrane Library:

#1 sorafenib:ti,ab,kw or sunitinib:ti,ab,kw or bevacizumab:ti,ab,kw or temsirolimus:ti,ab,kw or pazopanib:ti,ab,kw (Word variations have been searched)

#2 everolimus:ti,ab,kw or afatinib:ti,ab,kw or cabozanitinb:ti,ab,kw or IFN:ti,ab,kw or IL-2:ti,ab,kw (Word variations have been searched)

#3 nivolumab:ti,ab,kw or Immune checkpoint blockade:ti,ab,kw (Word variations have been searched)

#4 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees

#5 #1 or #2 or #3

#6 #4 and #5, Filter: Trials

Web of science

1 ((((((((((Topic: (sorafenib) OR Topic: (sunitinib)) OR Topic: (bevacizumab)) OR Topic: (pazopanib)) OR Topic: (temsirolimus)) OR Topic: (everolimus)) OR Topic: (afatinib)) OR Topic: (cabozanitinb)) OR Topic: (IFN)) OR Topic: (IL-2)) OR Topic: (nivolumab)) OR Topic: (Immune checkpoint blockade))

2 Title: (renal cell carcinoma) OR Title: (renal cancer) OR Title: (renal carcinoma) OR Title: (kidney cancer) OR Title: (kidney carcinoma)

3 #2 AND #1

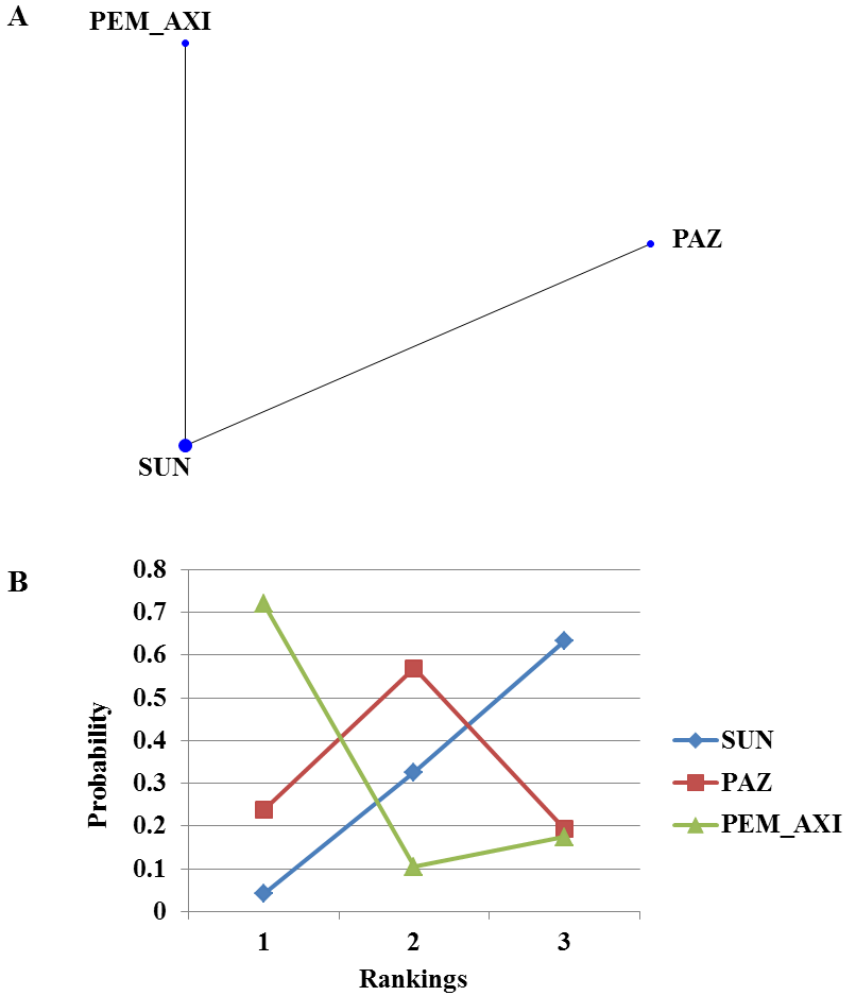
4 #2 AND #1 Document Types: CLINICAL TRIAL

ClinicalTrials.gov:

Category: “renal cell carcinoma OR renal cancer OR renal carcinoma OR kidney cancer OR kidney carcinoma, Studies With Results”

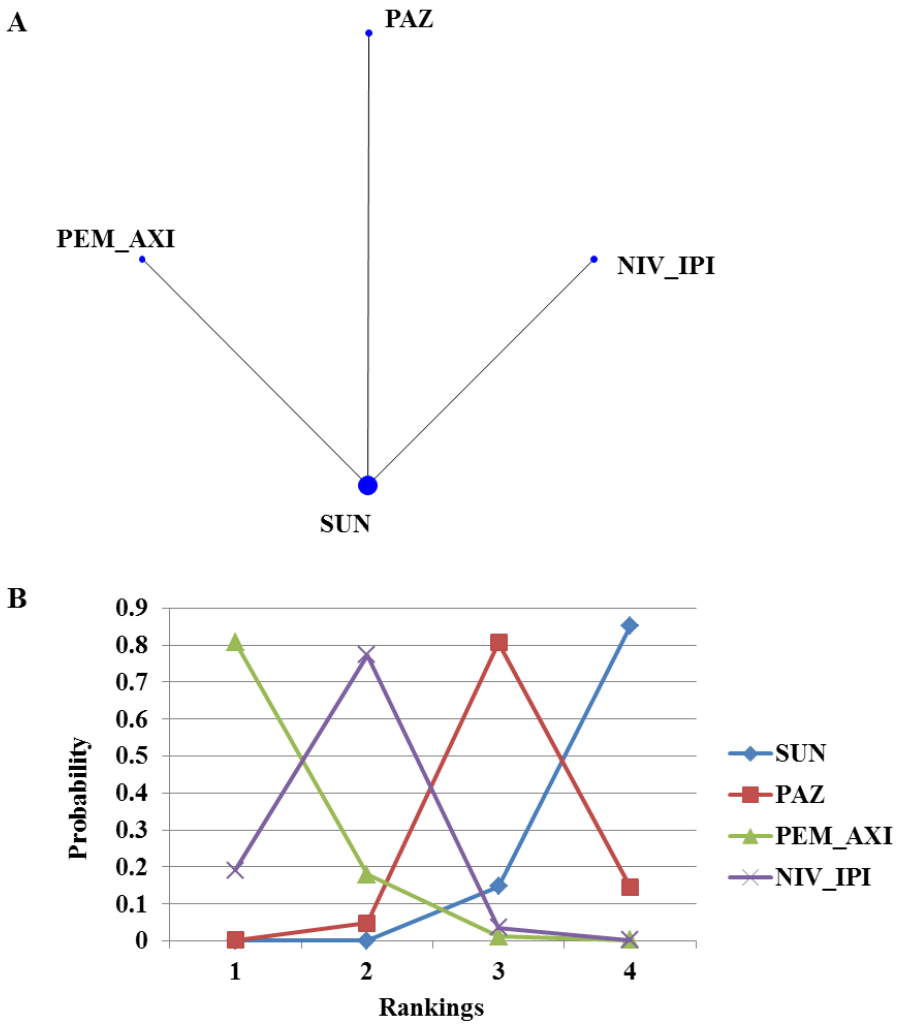
(http://clinicaltrials.gov/)

Appendix figure 1 Analysis of overall survival for patients with favorable-risk disease.



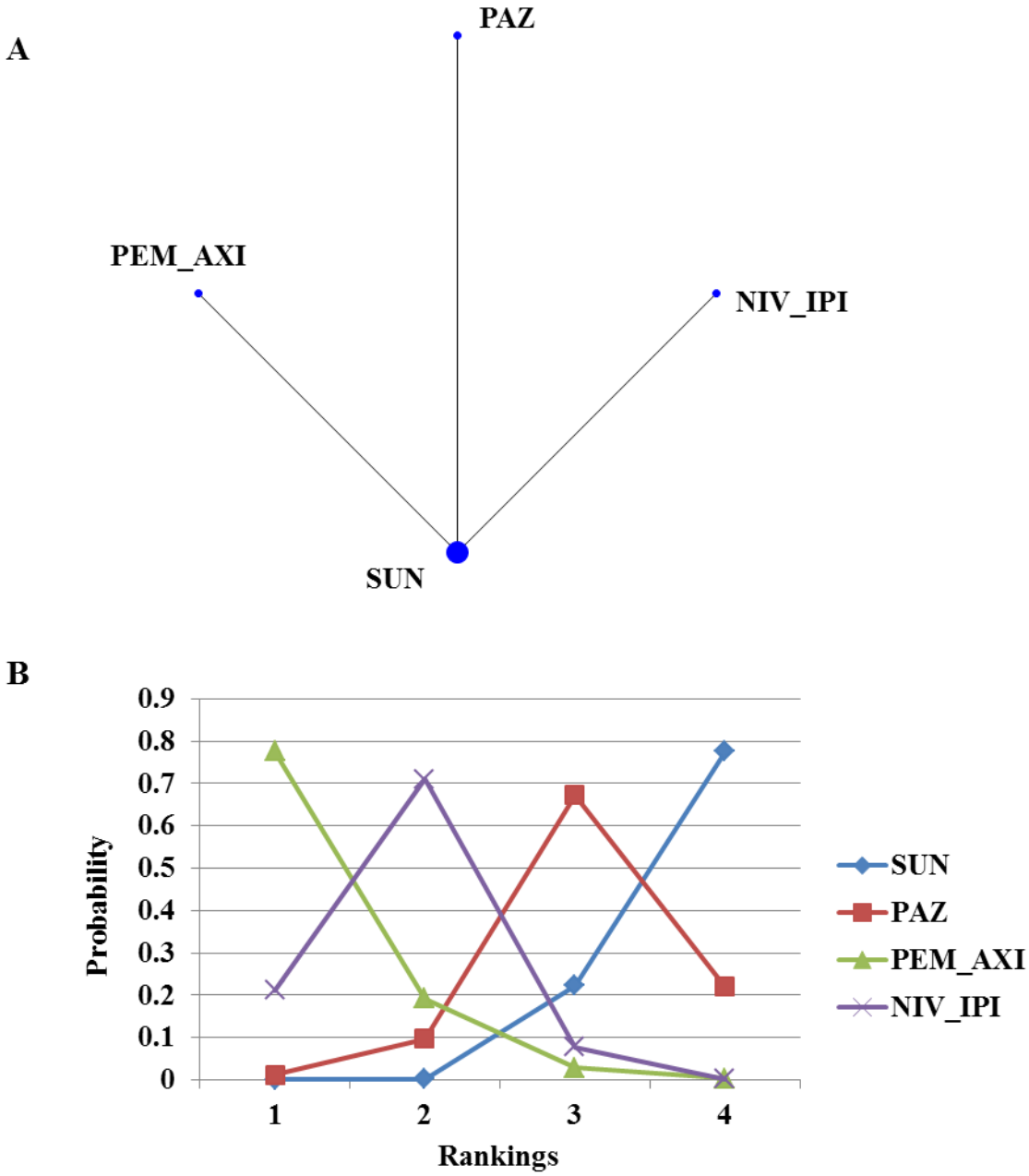
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the three treatments.SUN = sunitinib. PAZ = pazopanib. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 2 Analysis of overall survival for patients with intermediate-risk disease.



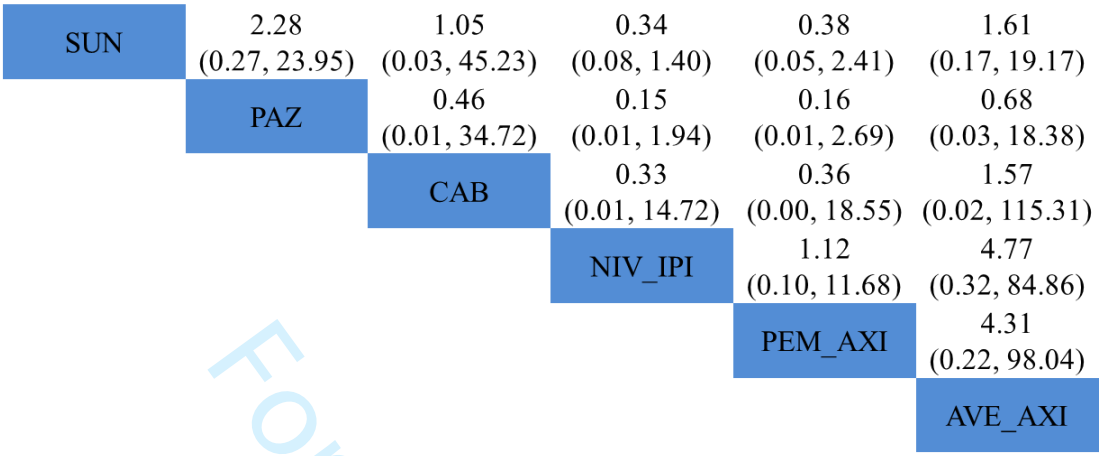
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the four treatments.SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 3 Analysis of overall survival for patients with poor-risk disease.



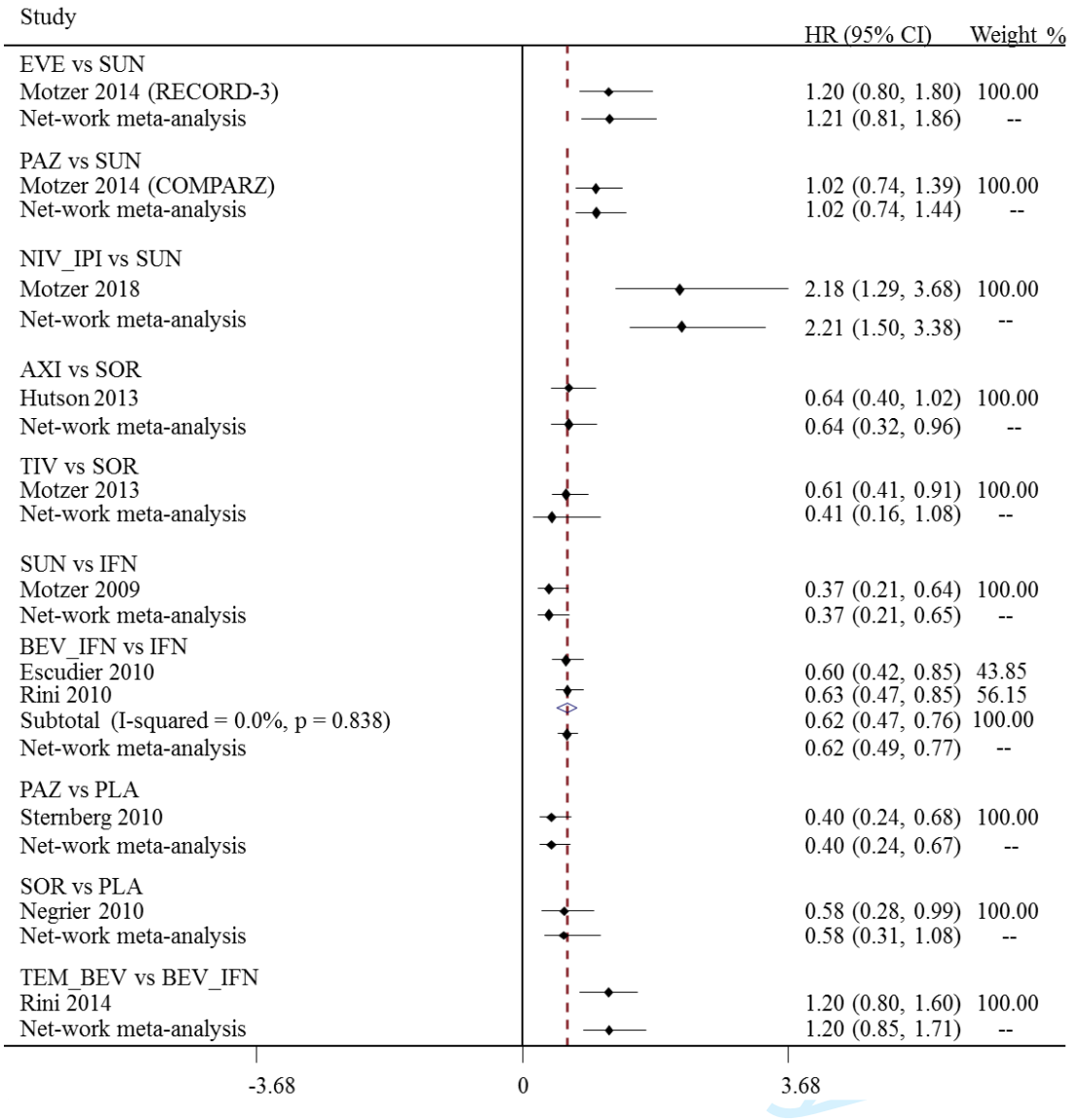
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the four treatments.SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 4: Pooled odds ratios for **overall adverse events** by Bayesian network meta-analysis



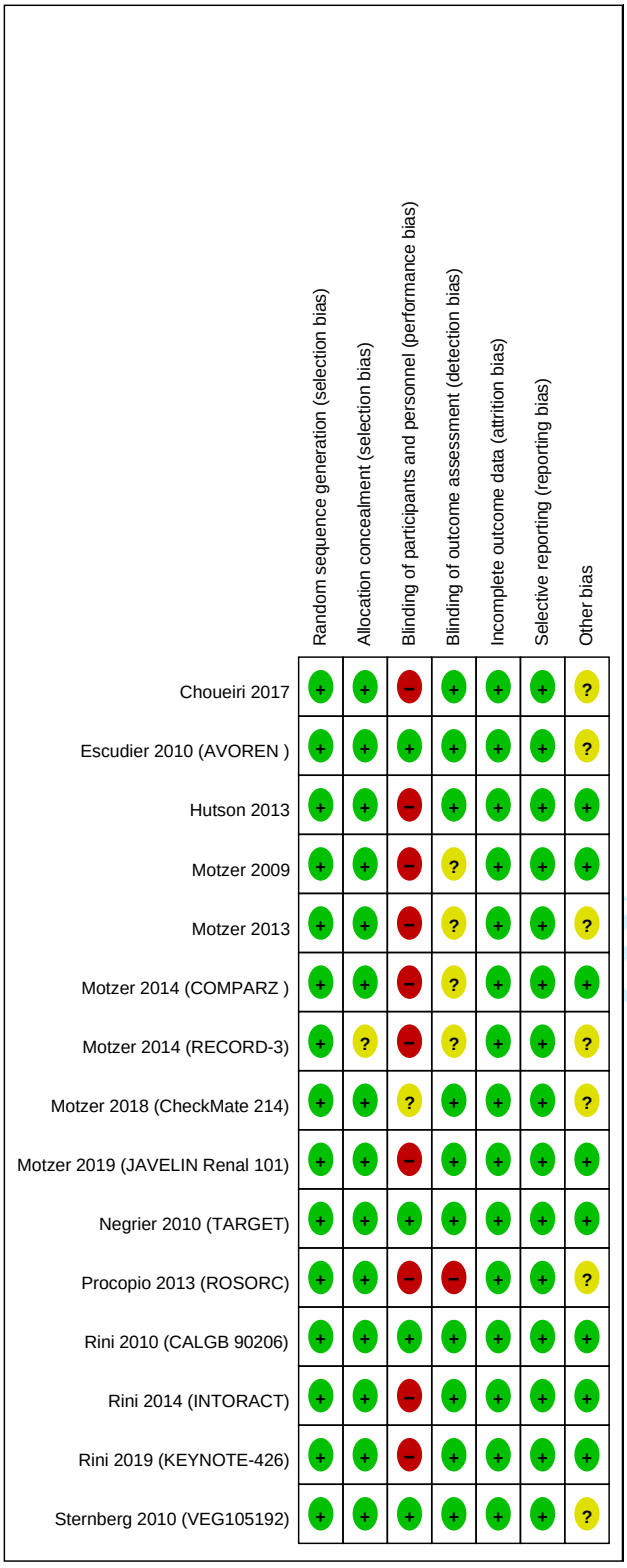
The column treatment is compared with the row treatment. ORs lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. Stepwise comparison of treatments did not find significant differences in rates of overall adverse events. SUN = sunitinib. PAZ = pazopanib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib.

Appendix figure 5 Pooled hazard ratios for progression-free survival by Bayesian network-analysis and traditional meta-analysis



HR = hazard ratio. CI=confidence interval for traditional meta-analysis and credible interval for Bayesian network meta-analysis. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab.

Appendix figure 6 Cochrane risk of bias tool assessment



Appendix Table 1: For advanced/metastatic RCC of favorable-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
PLA	**2.54 (1.37- 4.70)**	2.79 (0.005-4812)
IFN	**2.69 (1.54-4.67)**	2.57 (0.05-18.24)
SOR	1.47 (0.61-3.49)	1.56 (0.001-2735)
PAZ	1.02 (0.74-1.39)	1.03 (0.05-142.4)
AXI	0.93 (0.33-2.54)	0.95 (0.001-22200)
EVE	1.20 (0.80-1.80)	1.28 (0.03-66.05)
BEV_IFN	1.65 (0.90 -2.99)	1.54 (0.01-24.08)
TEM_BEV	1.98 (0.98 -3.96)	1.92 (0.02-155.90)
TIV	0.89 (0.34-2.35)	0.96 (0.001-11940)
NIV_IPI	**2.18 (1.47-3.25)**	2.16 (0.05-52.46)
PEM_AXI	0.64 (0.24-1.69)	0.64 (0.01-64.60)
AVE_AXI	**0.57 (0.34-0.96)**	0.57 (0.01-33.4)
DIC	9.68	11.19

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 2: For advanced/metastatic RCC of intermediate-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
PLA	**1.99 (1.29-3.14)**	2.00 (0.01-1366)
IFN	**2.57 (1.88-3.54)**	2.56 (0.02-283)
SOR	0.95 (0.47-1.91)	0.95 (0.002- 5382)
PAZ	0.98 (0.80-1.18)	0.98 (0.02- 94.94)
AXI	0.80 (0.36-1.81)	0.80 (0.001- 7618)
EVE	**1.50 (1.11-2.01)**	1.50 (0.02-121.20)
CAB	**0.63 (0.44-0.97)**	0.65 (0.01- 64.02)
BEV_IFN	**1.69 (1.18-2.41)**	1.60 (0.01- 895.10)
TEM_BEV	**1.88 (1.22-2.81)**	1.81 (0.002- 4299)
TIV	0.76 (0.36-1.65)	0.79 (0.001- 15210)
NIV_IPI	**0.66 (0.53-0.81)**	0.67 (0.01- 64.51)
PEM_AXI	**0.52 (0.35-0.81)**	0.52 (0.02-10.67)
AVE_AXI	**0.62 (0.47-0.83)**	0.60 (0.02-10.67)
DIC	1.97	2.92

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 3: For advanced/metastatic RCC of poor-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
IFN	1.87 (0.81- 4.32)	1.88 (0.03- 137.70)
EVE	1.73 (0.96- 2.99)	1.68 (0.02- 89.46)
CAB	0.74 (0.35-1.58)	0.75 (0.01- 54.64)
BEV_IFN	1.50 (0.60-3.62)	1.50 (0.01- 344.20)
TEM_BEV	1.20 (0.42-3.30)	1.22 (0.001- 1196)
NIV_IPI	**0.57 (0.43-0.76)**	0.57 (0.01- 36.17)
PEM_AXI	**0.43 (0.23-0.80)**	0.44 (0.01-53.85)
AVE_AXI	**0.55 (0.28-1.10)**	0.55 (0.01-43.91)
DIC	9.91	11.42

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon-α. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 4: Comparison of odds ratios (95% CI) for **high-grade adverse event** from consistency and inconsistency models.

Treatment compared with SUN	Consistency Model	Inconsistency Model
PLA	0.40 (0.02, 8.55)	0.39 (0.02, 8.91)
SOR	2.83 (0.06, 150.75)	2.65 (0.05, 160.98)
PAZ	1.07 (0.12, 9.19)	1.05 (0.12, 9.74)
TIV	1.98 (0.02, 201.54)	1.85 (0.02, 209.34)
CAB	0.92 (0.09, 8.13)	0.95 (0.09, 9.10)
SOR_IL-2	5.29 (0.06, 499.51)	4.89 (0.05, 495.91)
NIV_IPI	0.49 (0.05, 4.26)	0.50 (0.06, 4.41)
	1.30 (0.15, 12.14)	1.30 (0.15, 13.03)
	1.00 (0.11, 8.77)	0.98 (0.11, 8.56)
Random Effects Standard Deviation	0.85 (0.07, 1.69)	0.85 (0.07, 1.70)
Inconsistency Standard Deviation	NA	0.87 (0.04, 1.70)

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib.Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

Appendix Table 5: Comparison of odds ratios (95% CI) for **overall-grade adverse event** from consistency and inconsistency models.

Treatment compared with SUN	Consistency Model	Inconsistency Model
PAZ	2.28 (0.27, 23.95)	2.25 (0.30, 24.19)
CAB	1.05 (0.03, 45.23)	1.14 (0.03, 61.85)
NIV_IPI	0.34 (0.08, 1.40)	0.33 (0.08, 1.37)
PEM_AXI	0.38 (0.05, 2.41)	0.41 (0.06, 2.56)
AVE_AXI	1.61 (0.17, 19.17)	1.60 (0.15, 18.66)
Random Effects Standard Deviation	0.52 (0.04, 1.03)	0.53 (0.04, 1.02)
Inconsistency Standard Deviation	NA	0.53 (0.02, 1.02)

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Stepwise comparison of treatments did not find significant differences in rates of overall-grade adverse events.

Appendix Table 6: Comparison of results from primary analysis and sensitivity analysis for trials assessing approved targeted drugs.

Treatment	Primary Analysis PFS HR (95% CI) vs SUN	Sensitivity Analysis PFS HR (95% CI) vs SUN
PLA	**2.63 (1.47-4.71)**	**2.55 (1.38 -4.66)**
IFN	**2.70 (1.59-4.51)**	**2.71 (1.55 -4.71)**
SOR	1.47 (0.61-3.59)	1.48 (0.62 -3.55)
PAZ	1.03 (0.74-1.44)	1.02 (0.75 -1.41)
AXI	0.98 (0.36-2.76)	0.95 (0.35 -2.54)
EVE	1.21 (0.81-1.86)	1.20 (0.80-1.80)
BEV_IFN	1.66 (0.94 -2.88)	1.67 (0.92 -3.07)
TEM_BEV	**1.96 (1.04 -3.63)**	**2.00 (1.01 -4.03)**
TIV	0.92 (0.37-2.33)	**NA**
NIV_IPI	**2.21 (1.50-3.38)**	**2.18 (1.46-3.20)**

HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab. Bold type font indicates significant values.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

What's the optimum systemic treatment for advanced/metastatic renal cell carcinoma of favorable-, intermediate- and poor-risk, respectively? A systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034626.R2
Article Type:	Original research
Date Submitted by the Author:	04-May-2020
Complete List of Authors:	Cao, Guanghui; Henan Provincial People's Hospital Wu, Xiaoqiang; Henan Provincial People's Hospital Wang, Zhiwei; Henan Provincial People's Hospital Tian, Xiangyong; Henan Provincial People's Hospital Zhang, Chan; Henan Provincial People's Hospital, Department of Urology Wu, Xuan; Henan Provincial People's Hospital Zhang, Haotian; Henan Provincial People's Hospital Jing, Gaopeng; Henan Provincial People's Hospital Yan, Tianzhong; Henan Provincial People's Hospital,
Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology
Keywords:	Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY, IMMUNOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

What's the optimum systemic treatment for advanced/metastatic renal cell carcinoma of favorable-, intermediate- and poor-risk, respectively? A systematic review and network meta-analysis

Guanghui Cao, Xiaoqiang Wu, Zhiwei Wang, Xiangyong Tian, Chan Zhang, Xuan Wu, Haotian Zhang, Gaopeng Jing, Tianzhong Yan[#]

Department of Urology, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Zhengzhou 450003, China;

[#] Correspondence to Prof Tianzhong Yan PhD, Department of Urology, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Zhengzhou 450003, China.

E-mail address: ytz460@hotmail.com

Tel.: + 86 731 87160355; fax: + 86 431 87160356.

Abstract

Purpose: The optimum systemic therapies for advanced/metastatic renal cell carcinoma (RCC) of favorable-, intermediate-, and poor-risk have not been established. We aimed to compare and rank the effects associated with systemic therapies in the first-line setting.

Methods: We searched Pubmed, Cochrane databases, Web of Science, and ClinicalTrials.gov for randomized controlled trials (RCTs) published up to February 2020, of all available treatments for advanced/metastatic RCC. Analysis was done on a Bayesian framework.

Results: 15 unique RCTs including 8 995 patients were identified. For advanced/metastatic RCC of favorable-risk, avelumab plus axitinib was associated with a significantly higher improvement in progression-free survival (PFS) than sunitinib (HR 0.57, 95% CI 0.34-0.96). For intermediate-risk patients, cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.63, 95% CI 0.44-0.97; HR 0.66, 95% CI 0.53-0.81; HR 0.58, 95% CI 0.44-0.80; HR 0.62, 95% CI 0.47-0.83, respectively); pembrolizumab plus axitinib and nivolumab plus ipilimumab were associated with significantly higher improvement in overall survival (OS) than sunitinib (HR 0.53, 95% CI 0.34-0.81; HR 0.66, 95%CI 0.50-0.87, respectively). For poor-risk patients, nivolumab plus ipilimumab and pembrolizumab plus axitinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.43-0.76; HR 0.48, 95% CI 0.30-0.82, respectively); nivolumab plus ipilimumab and pembrolizumab plus axitinib were significantly more efficacious for OS than sunitinib (HR 0.57, 95% CI 0.39-0.883; HR 0.43, 95% CI 0.23-0.80, respectively). For OS, there were 81% and 78% probabilities that pembrolizumab plus axitinib was the best option for intermediate-risk and poor-risk patients, respectively.

Conclusion: Avelumab plus axitinib might be the optimum treatment for advanced/metastatic RCC of favorable-risk. Pembrolizumab plus axitinib might be the optimum treatment for intermediate-risk and poor-risk patients.

Keywords: renal cell carcinoma; systemic therapies; risk stratification; efficacy; safety.

Strengths and limitations of this study

► This is the first network analysis to compare systemic treatments for advanced/metastatic RCC separately by risk groups.

► Various statistical models were applied to synthesize data. The reliability and accuracy of results were corroborated by the low statistical heterogeneity and excellent model fit.

►Assessment of both efficacy and adverse events provides new insights into the benefit-harm balance of different systemic treatments.

►Main limitation lies in the reporting quality of trials included.

1. Introduction

Renal cell carcinoma (RCC) comprises approximately 90% of renal cancer, and represents approximately 2-3% of all new cancers worldwide [1]. It was estimated that there would be 62 700 new cases of renal cancer and 14 240 renal cancer-related deaths in the United States in 2016 [2]. In the European Union, new renal cancer cases and deaths in 2012 were approximately 84 400 and 34 700, respectively [3]. Up to 30% of patients were presented with advanced /metastatic RCC at the time of initial diagnosis [4 5]. Advanced/metastatic RCC is not a single condition, but is actually a heterogeneous group of conditions with different prognosis. The most widely accepted prognostic model is from the Memorial Sloan Kettering Cancer Center (MSKCC) and stratifies patients into favorable-, intermediate-, and poor-risk groups depending on the existence of well-characterized laboratory and clinical risk factors. The 2-year survival rates were 45%, 17%, and 3% for favorable-, intermediate-, and poor-risk groups, respectively [6]. In this systematic review, we focus on favorable-, intermediate-, and poor-risk patients with advanced/metastatic RCC.

In recent years, systemic treatment for advanced/metastatic RCC has changed from cytokines to drugs targeting angiogenesis. In 2007, results from two RCTs have been published reporting progress-free survival improvement of two newer targeted agents (sunitinib and sorafenib)[7 8]. To date, eight targeted drugs have been approved for treating advanced/metastatic RCC both in USA and Europe: five tyrosine kinase inhibitors (TKIs): sunitinib, sorafenib, pazopanib, cabozantinib, and axitinib; two mammalian target of rapamycin (mTOR) complex 1 kinase inhibitors: temsirolimus, and everolimus; and the recombinant humanized antivascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab combined with interferon-α (IFN-α). All eight targeted drugs showed significant survival benefit in randomized trials and established a prominent role in treating advanced/metastatic RCC [7 9-15]. More recently, immune checkpoint antibodies have introduced a new treatment option. CheckMate 214 reported that nivolumab plus ipilimumab was associated with a significantly higher overall survival than sunitinib in the first-line setting [16]. To further improve their efficacy, the combination of different classes of agents is

currently evaluated in clinical trials [17-20]. However, there are insufficient head-to-head RCTs to directly investigate the comparative effectiveness of all available therapies. Given the variety of treatment options for patients advanced/metastatic RCC and the limited evidence regarding the optimum treatment strategy, it is a challenge for clinicians to make the best decision.

In the present study, we performed a Bayesian network meta-analysis to compare first-line systemic treatments for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively. Network meta-analysis enables indirect comparisons based on a common comparator treatment when a head-to-head trial is unavailable and integrates direct and indirect comparisons to compare several treatment strategies while fully respecting randomization [21 22]. We aimed to summarize and compare the efficacy and safety associated with currently available systemic therapies for treating advanced/metastatic RCC of different risk categories using network meta-analysis.

2. Methods

2.1. Literature-search strategy

A comprehensive literature search was performed in Pubmed, Web of Science, ClinicalTrials.gov, and Cochrane databases for RCTs of systemic therapies of advanced/metastatic RCC (appendix for all search terms). All the reference lists of identified trials and related reviews were examined to find potential trials. The search was conducted in February 2020. There were no publication date or language restrictions.

2.2. Inclusion and exclusion criteria

All studies were selected according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria [23]. Studies were included if they satisfied three criteria: (1) the study enrolled patients who had histologically or cytologically confirmed advanced/metastatic RCC of favorable-, intermediate-, or poor-risk; (2) patients were randomly assigned to receive systemic

therapies alone or in combination. Relevant interventions included, but were not restricted to: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab, ipilimumab, axitinib, tivozanib, everolimus, temsirolimus, or bevacizumab plus IFN-α. Previous systemic therapy for advanced/metastatic RCC was not allowed; (3) one or more of the outcomes of interest mentioned below were reported. Nonoriginal articles, duplicate reports and non-RCTs were excluded.

2.3. Data Extraction and Quality Assessment

Two researchers (GH. Cao and XQ. Wu) examined the manuscripts of included trials independently, and extracted data into a structured form, including patient characteristics, treatment strategies, and interest outcomes [progress free survival (PFS), overall survival (OS), high-grade (grade ≥ 3) and overall drug-related adverse events]. The patient characteristics, treatment strategies, PFS and OS were extracted at the study-level for meta-analyses even if the patient-level were available. For drug-related adverse events, the patient-level data were extracted for meta-analyses. We gave priority to extracting data from intention-to-treat analyses. The methodological quality of included RCTs was assessed using the Cochrane risk of bias assessment tool [24]. Disagreement between investigators was resolved by consensus.

2.4. Data synthesis and analysis

First, we performed traditional meta-analyses to compare the treatments using Stata v.12 (StataCorp, College Station, TX, USA). We applied the chi-square test and the I^2 statistic to investigate the possibility of heterogeneity among studies. A P value < 0.10 or an I2 > 50% suggested the presence of substantial heterogeneity.

Second, we did Bayesian network meta-analyses. For meta-analysis of PFS and OS, the reported adjusted hazard ratios (HRs) with 95% CIs were applied as the outcome measure. For studies not reporting HRs, we calculated them from Kaplan-Meier curve and information on follow-up with the pragmatic approach reported by Tierney et al [25]. For drug-related adverse events, we calculated odds ratios (ORs) using the

available patient-level data abstracted from the trials. Both random-effects and fixed-effects models were performed for all Bayesian network meta-analyses [26]. Goodness of model fit was assessed using the deviance information criterion and between-study standard deviation [26 27]. Convergence was determined graphically according to the method described by Gelman *et al* [28].

It is believed that certain systemic treatments are effective in certain risk groups than others, for example sunitinib is more effective in favorable-risk patients and nivolumab plus ipilimumab is more effective in intermediate and poor-risk patients [29], suggesting that there is a treatment-by-risk group (favorable-, intermediate-, and poor-risk groups) interaction. Taking no account of this possible interaction in the analysis, transitivity assumption across all included trials would be violated. Therefore, we performed all network analyses separately by risk groups (favorable-, intermediate-, and poor-risk groups) according to the MSKCC or IMDC risk model to assure transitivity assumption.

One key assumption for network analysis is that direct and indirect comparisons do not disagree beyond chance [26 30]. To explore for evidence of inconsistency in the network, investigators compared the estimated treatment effects from the entire network with traditional pair-wise estimates [30]. Sensitivity analyses were performed restricted to trials that assessed approved systemic therapies (sunitinib, sorafenib, pazopanib, cabozantinib, axitinib, everolimus, temsirolimus, bevacizumab plus IFN-α, and nivolumab plus ipilimumab). Publication bias and small-study effects were assessed using funnel plots [31].

We performed the Bayesian network analysis using OpenBUGS version 3.2.2 for PFS, and Gemtc version 0.14.3 (van Valkenhoef *et al*, 2012) for adverse events. We performed fewer iterations for PFS to reduce computational burden without loss of convergence and model fit. For PFS, we applied 15 000 iterations obtained after a training phase of 10 000-iteration. In order to minimize autocorrelation, we applied a thinning interval of 50 for each chain. For adverse events, we applied the 60 000 iterations after a training phase of 40 000 iterations. The treatments were ranked in terms of PFS, OS, and high-grade AEs, respectively, using the surface under the

cumulative ranking curve (SUCRA) and the distribution of the ranking probabilities [32].

3. Results

3.1. Search results and study characteristics

The literature search yielded 2 017 potentially eligible studies, of which 1 873 were excluded based on screening titles and abstracts (Fig. 1). The full text of 144 remaining studies were analyzed, and finally 21 publications reporting 15 unique RCTs were included (Table), involving 8 995 participants randomly assigned to one of the 13 treatment strategies: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab plus ipilimumab, axitinib, tivozanib, everolimus, IFN-α, bevacizumab plus IFN-α, temsirolimus plus bevacizumab, avelumab plus axitinib, and pembrolizumab and axitinib. According to the MSKCC or IMDC criteria, there were 2 783, 5 474 and 721 participants had favorable-, intermediate-, and poor-risk disease, respectively.

The main characteristics of included RCTs are summarized in Table. The demographic characteristics of patients were well balanced across trials. Enrolled patients across trials were similar in terms of age, gender, and risk classification. Across trials, the median age of patients ranged from 58 to 64 years. The participants were predominantly male (71.7%, 6 451 of 8 995). The included trials were designed similarly. Median follow-up ranged from 10.7 to 58 months. The mean sample sizes were 100, 192 and 32 patients per group for favorable-, intermediate- and poor-risk subtypes, respectively. Thirteen trials selected for clear-cell carcinoma subtypes [10-12 15 16 33-40], and two trials also included small subsets of non-clear-cell histotypes, each comprising 11% and 14% of the study population, respectively [41 42]. All studies were two-arm trials. The dosages used in most of trials were within the recommended dose ranges.

In this network meta-analysis, results are reported based on fixed-effects models because they demonstrated better goodness of fit compared with random-effects

models. The results of random-effects models are available in appendix Table 1-5.

3.2. Progression-free survival

3.2.1. For advanced/metastatic RCC of favorable-risk, 13 trials enrolling 2 514 total patients reported adequate information on progression-free survival and contributed to network meta-analysis (Fig. 2A)[10-13 15 16 34-37 39-42]. Fig. 2B summarizes the results of the network meta-analysis for PFS. Compared with sunitinib, IFN-α and nivolumab plus ipilimumab were associated with significantly worse PFS (HR 2.69, 95% CI 1.54-4.67; and HR 2.18, 95% CI 1.47-3.25, respectively). Network meta-analysis showed that only avelumab plus axitinib was associated with a significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.34-0.96). Based on the results of ranking, there was a 45% chance that avelumab plus axitinib provided the greatest PFS benefit for patients with favorable-risk disease (SUCRA = 92.3%)(Fig. 2C).

3.2.2. For advanced/metastatic RCC of intermediate-risk, 14 trials enrolling 5 473 total patients contributed to the analysis of PFS (Fig. 3A) [10-13 15 16 33-37 39 40 42]. Network meta-analysis demonstrated that cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.63, 95% CI 0.44-0.97; HR 0.66, 95% CI 0.53-0.81; HR 0.58, 95% CI 0.44-0.80; HR 0.62, 95% CI 0.47-0.83, respectively). Everolimus, bevacizumab plus IFN-α, and temsirolimus plus bevacizumab were significantly less efficacious for PFS than sunitinib (HR 1.50, 95% CI 1.11-2.01; HR 1.69, 95% CI 1.18-2.41; HR 1.88, 95% CI 1.22-2.81, respectively) (Fig. 3B). Based on the analysis of ranking, pembrolizumab plus axitinib had the highest probability (49%) to be the best treatment for intermediate-risk patients (SUCRA = 90.7%). Avelumab plus axitinib and cabozantinib had a similar likelihood of being the second-best option for patients with intermediate-risk disease (Fig. 3C).

3.2.3. Based on data that was available for advanced/metastatic RCC of poor-risk, the

network involved seven trials comparing nine different treatments (721 total patients; Fig. 4A) [15 16 33-35 37 39 40 42]. Network meta-analysis demonstrated that nivolumab plus ipilimumab and pembrolizumab plus axitinib were associated with significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.43-0.76; HR 0.48, 95% CI 0.30-0.82, respectively) (Fig. 4B). On the base of ranking analysis, there was a 60% probability that pembrolizumab plus axitinib had the greatest PFS for poor-risk patients (SUCRA = 91.3%) (Fig. 4C).

3.3. Overall survival

Five RCTs reported OS according to risk subgroups, and data from three of them contributed to the network meta-analysis (572, 1801, and 407 patients for favorable-, intermediate-, and poor-risk, respectively)[16 38 39]. For advanced/metastatic RCC of favorable-risk, there is no significant OS benefit between sunitinib and pazopanib (HR 0.88, 95% CI 0.64-1.21) or pembrolizumab plus axitinib (HR 0.64, 95% CI 0.24-1.70) (Fig. 5A). For intermediate-risk patients, pembrolizumab plus axitinib and nivolumab plus ipilimumab were associated with significantly higher improvement in OS than sunitinib (HR 0.53, 95% CI 0.34-0.81; HR 0.66, 95% CI 0.50-0.87, respectively)(Fig. 5B). For advanced/metastatic RCC of poor-risk, pembrolizumab plus axitinib and nivolumab plus ipilimumab were significantly more efficacious for OS than sunitinib (HR 0.43, 95% CI 0.23-0.80; HR 0.57, 95% CI 0.39-0.83, respectively) (Fig. 5C). Based on the results of ranking, there were 81% and 78% probabilities for pembrolizumab plus axitinib to be the best choice for intermediate- and poor-risk patients, respectively (SUCRA =93.1% ; SUCRA= 91.4%, respectively) (appendix Fig.1-3).

3.4. Adverse events

Nine trials contributed to our analysis of overall and high-grade drug-related adverse events [10 11 13 15 16 36 39-41]. All the nine trials did not provide adverse events data for different risk groups, so we extracted a summary of adverse event data. Results of comparisons of adverse events of nine systemic treatments are presented in

Fig. 6 and appendix Fig. 4 Stepwise comparison of all the seven therapies did not find significant differences in rates of high-grade or overall adverse events. The most common adverse events included diarrhea, hypertension, fatigue, and decreased appetite.

3.5. Network assumptions, sensitivity analysis, publication bias, and risk of bias

Consistencies between direct and indirect evidence were noted for any comparisons (appendix Fig. 5 and appendix Table 1-5). Results from the sensitivity analyses were in line with the primary analysis (appendix Table 6).The comparison-adjusted funnel plot (Fig. 7) for PFS was largely symmetric, indicating no obvious small-study effects and publication bias. The methodological quality was moderate in the included studies (appendix Fig. 6). All trials were thought to have low risk of bias for random sequence generation, incomplete outcome data, and selective reporting of outcomes. Ten trials had evidence of high risk of bias for masking [12 13 15 35-37 39-42].

4. Discussion

Our network meta-analysis of 15 RCTs including 8 995 individuals assessed the efficacy and safety of all major systematic therapies for the treatment of advanced/metastatic RCC in the first-line setting. Findings of this meta-analysis might help to choose among systemic agents for the management of patients with previously untreated advanced/metastatic RCC. In terms of PFS, avelumab plus axitinib was most likely to be the best treatment regimen for advanced/metastatic RCC of favorable-risk, and pembrolizumab plus axitinib seemed to be the most efficacious treatment strategy for patients with intermediate- and poor-risk. In terms of OS, there were no significant differences among systematic therapies for advanced/metastatic RCC of favorable-risk, and pembrolizumab plus axitinib was probably to be the best option for patients with intermediate- and poor-risk. In terms of drug-related adverse events, there were no significant differences among systemic therapies.

In RCC with clear cell subtype, hypoxia-inducible factor (HIF) accumulation due to loss of von Hippel-Lindau (VHL) leads to overexpression of VEGF and platelet

derived growth factor (PDGF), which promotes tumor angiogenesis [43 44]. This process substantially makes a contribution to the development and progression of clear cell RCC. Inhibiting the VEGF signaling has been supposed as the key mechanism for antitumor effects in clear cell RCC. To date, eight targeted drugs have been approved for treating advanced RCC: sunitinib, sorafenib, pazopanib, cabozantinib, axitinib, everolimus, temsirolimus, and bevacizumab (in combination with IFN-α).

As shown in this analysis, for patients with intermediate-risk, sunitinib resulted in a significant PFS benefit compared with everolimus. The varied clinical benefit could be associated with mechanisms of action of TKI and mTOR inhibitor. Sunitinib not only inhibit VEGF receptors -1, -2, and -3, which may be the most clearly relevant targets in RCC so far, but also exhibit potent activity against PDGF receptor[11 45]. It has been reported that PDGF plays a critical role in the recruitment of pericytes to sprouting tumor vessels, and pericyte-covered vessels are more likely resistant to anti-vascular therapy than those pericyte-negative vessels [46 47]. The mTOR complex is the upstream of an intracellular signaling network regulating cell growth and angiogenesis, and it plays a key role in the pathogenesis of advanced/metastatic RCC [48]. It has been demonstrated that rapamycin analogs, including everolimus and temsirolimus, inhibit only one of two signaling complexes of mTOR [49]. The mTORC1 signaling is potently inhibited by everolimus and temsirolimus, while the mTORC2 signaling is not [50]. Consequently, one downstream signaling of mTOR activation is unopposed. The relatively unsatisfactory efficacy should disable the mTOR inhibitors as more suitable therapies for the treatment of advanced/metastatic RCC than TKIs. Regarding TKIs, our results suggest that sunitinib was most likely to be the best treatment regimen for patients with favorable-risk disease.

A potentially additive benefit from combinations of targeted drugs has been suggested on the basis that they inhibit separate cellular pathways. However, our results show that temsirolimus plus bevacizumab, and bevacizumab plus IFN-α provide little survival benefit compared with sunitinib, further confirming absence of evidence that combination treatment simultaneously inhibiting both VEGF and

mTOR signaling results in therapeutic synergy [18 20 37].

Immune checkpoint antibodies block the inhibitory T-cell receptor programmed death-1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4)-signaling to augment tumor specific immune response [51]. Nivolumab (an anti-PD-1 antibody) is approved for the treatment of advanced RCC in the second line setting. Ipilimumab (an anti- CTLA-4 antibody) is approved for the treatment of advanced melanoma. Nivolumab plus ipilimumab has been reported significant efficacy in multiple tumor types [52 53]. In this analysis, pembrolizumab plus axitinib appeared to be the optimum treatment for intermediate- and poor-risk patients. Single-agent anti-tumor activity of pembrolizumab and axitinib for mRCC has been reported in previous studies [12 54]. Accordingly, axitinib in combination with pembrolizuma was assessed and contributed to objective response rate in 73% patients in a phase 1b trial [55]. Our result was in consistent with results of KEYNOTE-426 trial, demonstrating that pembrolizumab plus axitinib resulted in significant OS and PFS benefit compared with sunitinib [39]. In addition, the survival benefit of pembrolizumab plus axitinib was observed independent of PD-L1 status [39].

Pembrolizumab plus axitinib is a combination of anti- PD-1 monoclonal antibody and VEGF receptor TKI. Immune checkpoint inhibitors (ICI) block the inhibitory T-cell receptor PD-1 or CTLA-4-signaling to augment tumor specific immune response [51]. Besides of antiangiogenic effects, VEGF inhibition could enhance the recruitment and infiltration of immune cells into the tumors [56 57]. It's reported that simultaneous blockade of PD-1 and VEGF receptor-2 induced decreased tumor neovascularization and tumor inhibition in a murine model [58]. These studies suggested that the combination of ICI and VEGF receptor inhibitors could provide enhanced benefit for mRCC. Recently, in addition to pembrolizumab plus axitinib, avelumab (anti-PD-L1 antibody) plus axitinib, and atezolizumab (anti-PD-L1 antibody) plus bevacizumab were respectively assessed in two phase 3 RCTs (IMmotion 151 and JAVELIN Renal 101), and both of them showed significant survival benefit for mRCC compared with sunitinib [39 59].However, there is no head-to-head trial comparing combinations of ICI and VEGF receptor inhibitors

inhibitors (pembrolizumab plus axitinib, aveluma plus axitinib, and atezolizumab plus bevacizumab) directly. In consistent with our previous study, the present analysis revealed that pembrolizumab plus axitinib presented the highest OS benefit for intermediate- and poor-risk patients. For advanced/metastatic RCC of favorable-risk, only avelumab plus axitinib was associated with a significantly higher improvement in PFS than sunitinib, suggesting avelumab plus axitinib might be the optimum treatment for favorable-risk patients. Considering patients continued to be followed for OS in the JAVELIN Renal 101 trial [40], the real OS benefit for avelumab plus axitinib over sunitinib requires additional follow-up.

Recently, several network meta-analyses were attempted to investigate the comparative effects of different systemic agents for treatment of advanced/metastatic RCC [60-63]. However, trials included in the meta-analyses enrolled patients with different risk groups. The analysis used aggregate data and did not perform subgroup analysis based on risk strata. In the present study, we performed a network meta-analysis to compare first-line systemic treatments for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively， thus providing physicians with the optimal treatment for different risk groups.

The strengths of our study are as follows. To the best of our knowledge, this study is the first network analysis to compare systemic treatments for advanced/metastatic RCC separately by risk groups. We applied multiple rigorous search strategies to retrieve all potentially eligible RCTs. In the present study, we comprehensively compared and ranked all available first-line systemic therapies for advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively, thus providing physicians with an overall appraisal of systemic therapies for different risk groups. In addition, we used Bayesian network meta-analysis to synthesize data. This approach provides indirect effect estimates in the absence of head-to-head trial and incorporates all available information from RCTs while fully maintaining randomization [21 22]. We applied various statistical models to increase reliability of the results. Results were consistent across all analyzed outcomes. Moreover, the reliability and accuracy of results were corroborated by the low statistical

heterogeneity and excellent model fit. Finally, assessment of both efficacy and adverse events provides new insights into the benefit-harm balance of different systemic treatments.

However, the limitations of our study must be taken into account. The major limitation of this network meta-analysis lies in the reporting quality of trials reviewed. Ten included trials were not masked, which might affect the validity of our findings. In addition, three included trials (CABOSUN, ROSORC, and RECORD-3) are phase 2 RCTs with smaller sample size, and they may be less authoritative compared with phase 3 RCTs. Moreover, most of the trials did not perform the analysis of OS in risk subgroupd, which made it impossible to assess the OS benefits of all the existing treatments for different risk patients. In addition, this meta-analysis was conducted based on summary statistics rather than individual patient level data. There might be some confounding factors (*e.g.*, ethnic origin, prior nephrectomy, *etc*.) at the individual patient level that might influence the benefit of systemic treatments, but were not available; therefore analyses adjusted for these factors were impossible in our network meta-analysis. Access to patient-level longitudinal data would allow us to establish more robust and accurate conclusions in specific subgroups of patients. Moreover, the length of follow-up varied across studies, resulting in potential variations in survival benefits and adverse events. Due to only eight trials reporting median follow-up, sensitivity analyses adjusted for this factor were impossible. Moreover, individual dosage varied across studies and data were too sparse to investigate effects of different schedules, which might somewhat affect the generalisability of our findings. Since the analysis was based on highly selected RCTs and the results were based on fixed-effects models, findings in this analysis may not be entirely generalized to real-world practice. Finally, findings in this meta-analysis were mainly based on patients with clear-cell advanced RCC, thus no robust recommendations can be provided for non-clear-cell subtypes. Two trials included small subsets of non-clear-cell histotypes (11% and 14% of the study population), which might somewhat damage the results of our analysis.

5. Conclusions

Our network meta-analysis suggested that: avelumab plus axitinib might be the optimum treatment for advanced/metastatic RCC of favorable-risk; pembrolizumab plus axitinib was most likely to be the best option for intermediate- and poor-risk patients. Further well-designed, large-scale RCTs are required to confirm and update the findings of this analysis.

Author Contributions

G-HC and X-QW conceived and designed the meta-analysis, Z-ZW and X-YT identified and acquired reports of trials, and extracted data. XW and H-TZ analyzed and interpreted the data. CZ and G-PJ contacted authors of trials for additional information. G-HC and X-QW drafted the manuscript. T-ZY critically reviewed the manuscript. All authors approved the final submitted version of the report.

Fundings: This research was supported by the Henan Provincial Medical Scientific and Technological Research Project (Grant No. 201702191). The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflicts of Interest: None declared.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research.

References:

1. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67(5):913-24.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7-30.
3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374-403.
4. Janzen NK, Kim HL, Figlin RA, et al. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003;30(4):843-52.
5. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005;353(23):2477-90.
6. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies Against Advanced Renal Cell Carcinoma. Journal of Clinical Oncology 2002;20(1):289-96.
7. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356(2):115-24.
8. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356(2):125-34.
9. Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008;26(33):5422-8.
10. Negrier S, Jager E, Porta C, et al. Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. Med Oncol 2010;27(3):899-906.
11. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28(6):1061-8.
12. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol 2013;14(13):1287-94.
13. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369(8):722-31.
14. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27(8):1280-9.

15. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. Journal of Clinical Oncology 2017;35(6):591-97.
16. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378(14):1277-90.
17. Jonasch E, Corn P, Pagliaro LC, et al. Upfront, randomized, phase 2 trial of sorafenib versus sorafenib and low-dose interferon alfa in patients with advanced renal cell carcinoma: clinical and biomarker analysis. Cancer 2010;116(1):57-65.
18. Negrier S, Gravis G, Perol D, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol 2011;12(7):673-80.
19. Procopio G, Verzoni E, Bracarda S, et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: the ROSORC trial. Br J Cancer 2011;104(8):1256-61.
20. Ravaud A, Barrios CH, Alekseev B, et al. RECORD-2: phase II randomized study of everolimus and bevacizumab versus interferon alpha-2a and bevacizumab as first-line therapy in patients with metastatic renal cell carcinoma. Ann Oncol 2015;26(7):1378-84.
21. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331(7521):897-900.
22. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23(20):3105-24.
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of internal medicine 2009;151(4):W65-94
24. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343.
25. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
26. Dias S, Welton NJ, Sutton AJ, et al. A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. Medical Decision Making 2014.
27. Spiegelhalter DJ, Best NG, Carlin BP, et al. Bayesian measures of model complexity and fit. Journal of The Royal Statistical Society Series B-statistical Methodology 2002;64(4):583-639.
28. Gelman A, Rubin DB. Markov chain Monte Carlo methods in biostatistics. Stat Methods Med Res 1996;5(4):339-55.
29. Powles T, Albiges L, Staehler M, et al. Updated European Association of Urology Guidelines Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. Eur Urol 2017;73(3):311-15.
30. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making 2013;33(5):641-56.

31. Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8(10):e76654.
32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64(2):163-71.
33. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 2010;28(13):2144-50.
34. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol 2010;28(13):2137-43.
35. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27(22):3584-90.
36. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013;31(30):3791-9.
37. Rini BI, Bellmunt J, Clancy J, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. J Clin Oncol 2014;32(8):752-9.
38. Motzer RJ, Hutson TE, McCann L, et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. N Engl J Med 2014;370(18):1769-70.
39. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380(12):1116-27.
40. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380(12):1103-15.
41. Procopio G, Verzoni E, Bracarda S, et al. Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): final results of the ROSORC trial. Ann Oncol 2013;24(12):2967-71.
42. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32(25):2765-72.
43. Patard JJ, Rioux-Leclercq N, Fergelot P. Understanding the importance of smart drugs in renal cell carcinoma. Eur Urol 2006;49(4):633-43.
44. Costa LJ, Drabkin HA. Renal cell carcinoma: new developments in molecular biology and potential for targeted therapies. Oncologist 2007;12(12):1404-15.
45. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res

2003;9(1):327-37.
46. Benjamin LE, Hemo I, Keshet E. A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF. Development 1998;125(9):1591-8.
47. Gee MS, Procopio WN, Makonnen S, et al. Tumor vessel development and maturation impose limits on the effectiveness of anti-vascular therapy. Am J Pathol 2003;162(1):183-93.
48. Creighton CJ, Morgan M, Gunaratne PH, et al. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature 2013;499(7456):43-49.
49. Loewith R, Jacinto E, Wullschleger S, et al. Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. Mol Cell 2002;10(3):457-68.
50. Inoki K, Guan KL. Complexity of the TOR signaling network. Trends Cell Biol 2006;16(4):206-12.
51. Ribas A. Tumor immunotherapy directed at PD-1. N Engl J Med 2012;366(26):2517-9.
52. Hammers HJ, Plimack ER, Infante JR, et al. Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. J Clin Oncol 2017;35(34):3851-58.
53. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17(7):883-95.
54. McDermott DF, Lee J-L, Szczylik C, et al. Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (accRCC): Results from cohort A of KEYNOTE-427. Journal of Clinical Oncology 2018;36(15_suppl):4500-00.
55. Atkins MB, Plimack ER, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncol 2018;19(3):405-15.
56. Shrimali RK, Yu Z, Theoret MR, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010;70(15):6171-80.
57. Huang Y, Yuan J, Righi E, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proceedings of the National Academy of Sciences of the United States of America 2012;109(43):17561-6.
58. Yasuda S, Sho M, Yamato I, et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo. Clinical and experimental immunology 2013;172(3):500-6.
59. Rini BI, Powles T, Atkins MB, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet 2019;393(10189):2404-15.
60. Wallis CJD, Klaassen Z, Bhindi B, et al. First-line Systemic Therapy for Metastatic Renal Cell

Carcinoma: A Systematic Review and Network Meta-analysis. Eur Urol 2018;74(3):309-21.

61. Wang J, Li X, Wu X, et al. Role of immune checkpoint inhibitor-based therapies for metastatic renal cell carcinoma in the first-line setting: A Bayesian network analysis. EBioMedicine 2019;47:78-88.
62. Hahn AW, Klaassen Z, Agarwal N, et al. First-line Treatment of Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. European urology oncology 2019;2(6):708-15.
63. Karner C, Kew K, Wakefield V, et al. Targeted therapies for previously treated advanced or metastatic renal cell carcinoma: systematic review and network meta-analysis. BMJ Open 2019;9(3):e024691.

Table: Studies included in the multiple-treatments meta-analysis

Study	Number of patients	Age (years) median(range)	Sex (% male)	MSKCC (%)			Median PFS in months (95% CI)	Hazard ratio (95% CI)
				Favorable	Intermediate	Poor		
Motzer 2014 (RECORD-3)								
Everolimus	238	62 (20-89)	69.7	29	56	15	7.9	1.4 (1.2-1.8)
Sunitinib	238	62 (29-84)	73.9	30	56	14	10.7	1 (Ref)
Motzer 2014 (COMPARZ)								
Pazopanib	557	61 (18-88)	71	27	58	12	8.4 (8.3-10.9)	1.05 (0.90-1.22)
Sunitinib	553	62 (23-86)	75	27	59	9	9.5 (8.3-11.1)	1 (Ref)
Rini 2014 (INTORACT)								
Temsirolimus plus bevacizumab	400	59 (22-87)	72	28	65	8	9.1 (8.1-10.2)	1.1 (0.9-1.3)
Bevacizumab plus IFN-α	391	58 (23-81)	69	27	65	8	9.3 (9.0-11.2)	1 (Ref)
Pizzocaro 2013 (ROSORC)								
Sorafenib plus interleukin-2	66	64 (57-69) *	79	55	41	5	NA	NA
Sorafenib	62	62 (52-69) *	69	55	39	6	NA	NA
Hutson 2013								
Axitinib	192	58 (23-83)	70	49	44	4	10.1 (7.2-12.1])	0.77 (0.56-1.05)
Sorafenib	96	58 (20-77)	77	55	42	2	6.5 (4.7-8.3)	1 (Ref)
Motzer 2013								
Tivozanib	260; treatment-naive 181	59 (23-83)	71	27	67	7	12.7 (9.1-15.0)	0.756 (0.580-0.985)
Sorafenib	257; treatment naive 181	59 (23-85)	74	34	62	4	9.1 (7.3-10.8)	1 (Ref)
Sternberg 2010 (VEG105192)								
Pazopanib	290; treatment naive 155	59 (28-82)	68	36	56	4	11.1	0.40 (0.27-0.60)
Placebo	n = 145; treatment naive 78	62 (25-81)	74	40	51	6	2.8	1 (Ref)
Motzer 2009								
Sunitinib	375	62 (27-87)	71	38	56	6	11 (11-13)	0.539 (0.451-0.643)
IFN-α	375	59 (34-85)	72	34	59	7	5 (4-6)	1 (Ref)
Ngarier 2010 (TARGET)								
Sorafenib	451; treatment-naive 77	60	63.6	53.2	46.8	0	5.8	0.48 (0.32-0.73)
Placebo	452; treatment-naive 84	60.5	69	45.2	54.8	0	2.8	1 (Ref)
Rini 2010 (CALGB 90206)								

Bevacizumab plus IFN-α	369	61 (56-70)	73	26	64	10	8.5 (7.5-9.7)	0.71 (0.61-0.83)
IFN-α	363	62 (55-70)	66	26	64	10	5.2 (3.1-5.6)	1 (Ref)
Escudier 2010 (AVOREN)								
Bevacizumab plus IFN-α	327	61 (30–82)	68	27	56	9	10.2	0·61 (0·51-0·73)
IFN-α	322	60 (18–81)	73	29	56	8	5.4	1 (Ref)
								Continued
Motzer 2018 (CheckMate 214)								
Nivolumab plus Ipilimumab	550	62 (26-85)	75	23	61	17	11.6 (8.7–15.5)	0.82(0.64-1.05)‡
Sunitinib	546	62 (21-85)	72	23	61	16	8.4 (7.0–10.8)	1 (Ref)
Choueiri 2017								
Cabozantinib	79	63 (40-82)	83.5	0	81.0§	19.0§	8.2 (6.2 to 8.8)	0.66 (0.46-0.95)
Sunitinib	78	64(31-87)	73.1	0	80.8§	19.2§	5.6 (3.4 to 8.1)	1 (Ref)
Motzer 2019 (JAVELIN Renal 101)								
Avelumab plus Axitinib	442	62 (29-83)	71.5	21.7	64.0	11.5	13.8 (11.1-NE)	0.69 (0.56-0.84)
Sunitinib	444	61 (27-88)	77.5	22.5	66.0	10.1	8.4 (6.9-11.1)	1 (Ref)
Rini 2019 (KEYNOTE-426)								
Pembrolizumab and Axitinib	432	62 (30-89)	71.3	31.9§	55.1§	13§	15.1 (12.6-17.7)	0.69 (0.57-0.84)
Sunitinib	429	61 (26-90)	74.6	30.5§	57.3§	12.1§	11.1 (8.7-12.5)	1 (Ref)

IFN-α = interferon-α; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; CI = confidence interval; AE = adverse event; NA=not available; Ref = reference group (hence hazard ratio set to 1);

* interquartile range; † mean; ǂ 99.1% CI; § IMDC risk group, International Metastatic Renal Cell Carcinoma Database Consortium

Legends for Figures

Fig. 1 - Literature search and selection

Fig. 2 - Analysis of progression-free survival for patients with favorable-risk disease.

(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of PFS, among the 13 treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI =

axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

Fig. 3 - Analysis of progression-free survival for patients with intermediate-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

Fig. 4 - Analysis of progression-free survival for patients with poor-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon-α. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

Fig.5- Analysis of overall survival for patients with favorable- risk (A), intermediate- risk (B), and poor-risk (C). HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib.

Fig. 6 - Pooled odds ratios for high-grade adverse events.

The column treatment is compared with the row treatment. Odds ratios lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib. Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis for hazard ratios of progression-free survival

SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

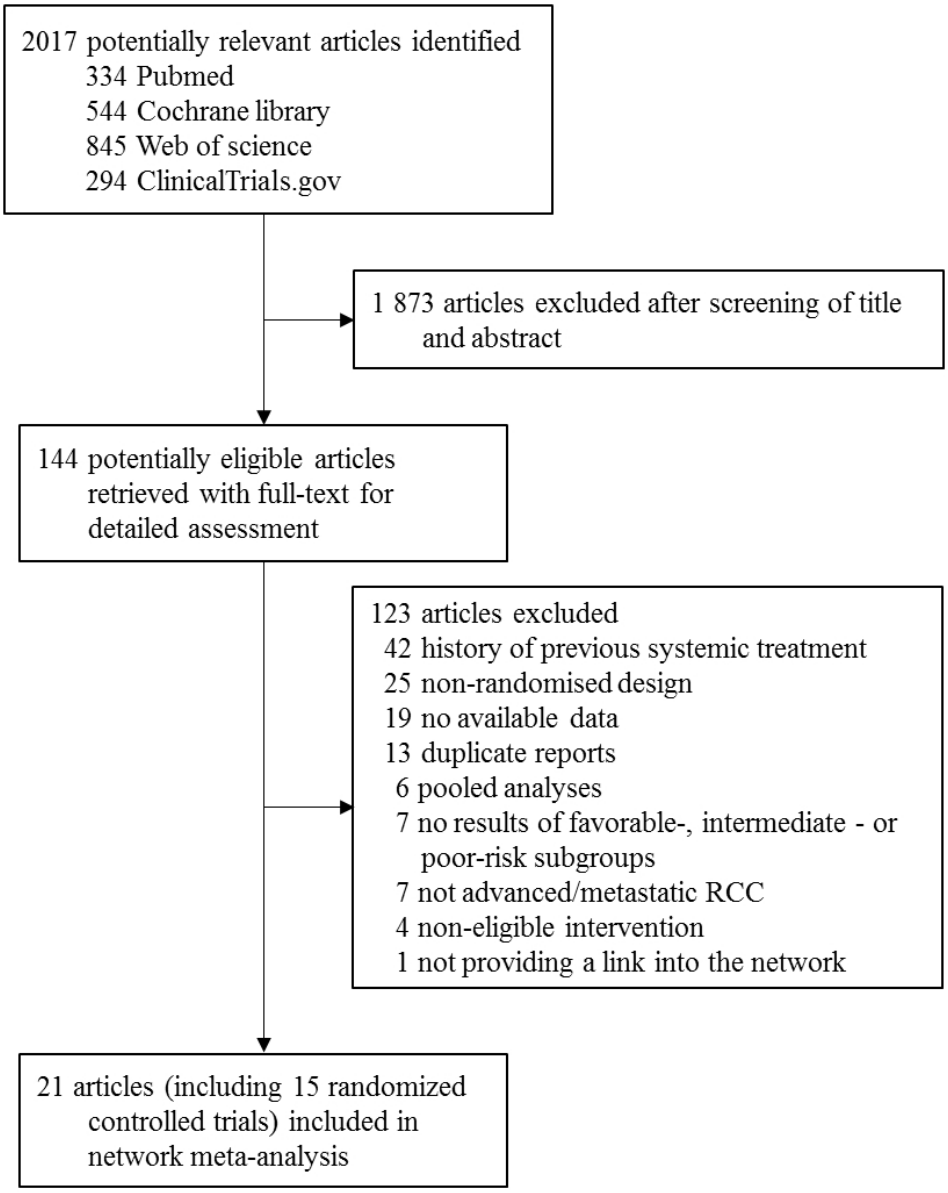


Fig. 1 - Literature search and selection

140x174mm (150 x 150 DPI)

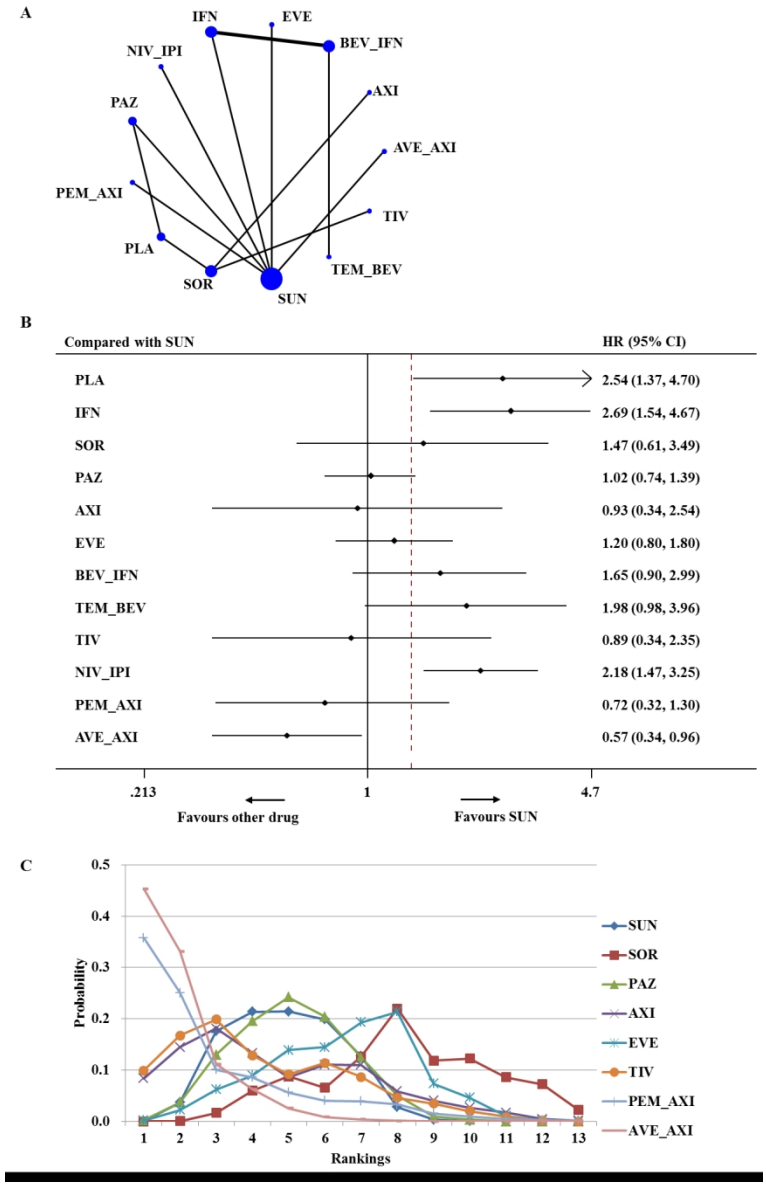


Fig. 2 - Analysis of progression-free survival for patients with favorable-risk disease.
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of PFS, among the 13 treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

220x347mm (150 x 150 DPI)

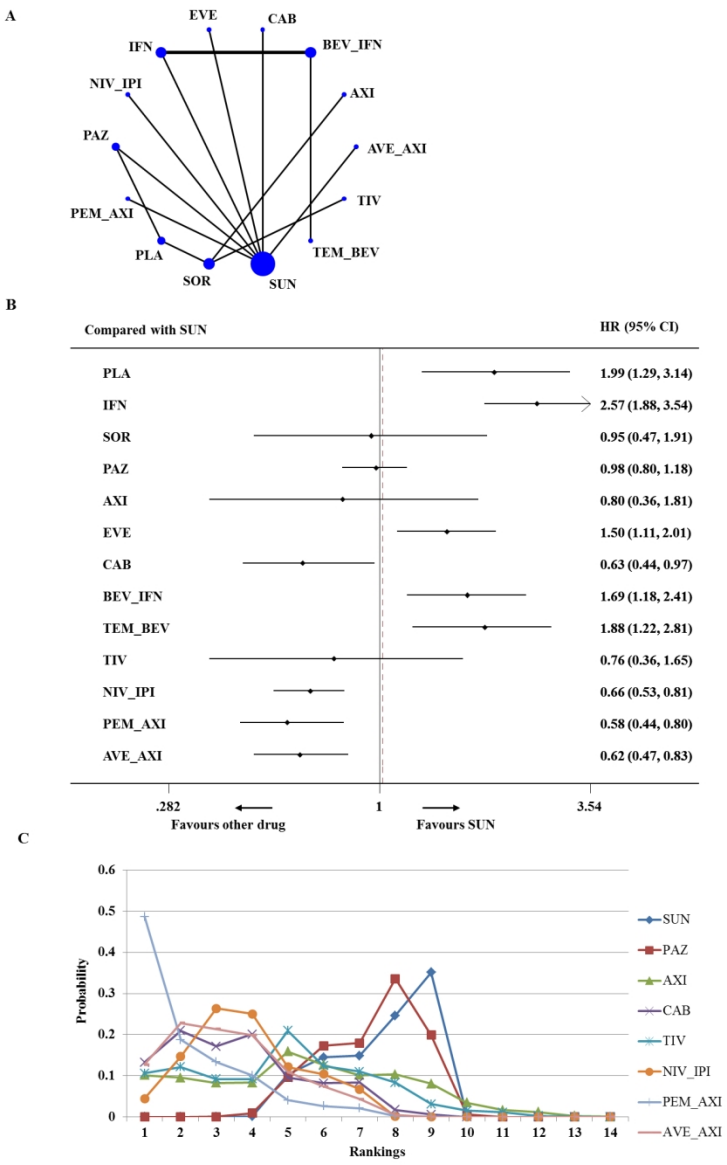


Fig. 3 - Analysis of progression-free survival for patients with intermediate-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

235x369mm (150 x 150 DPI)

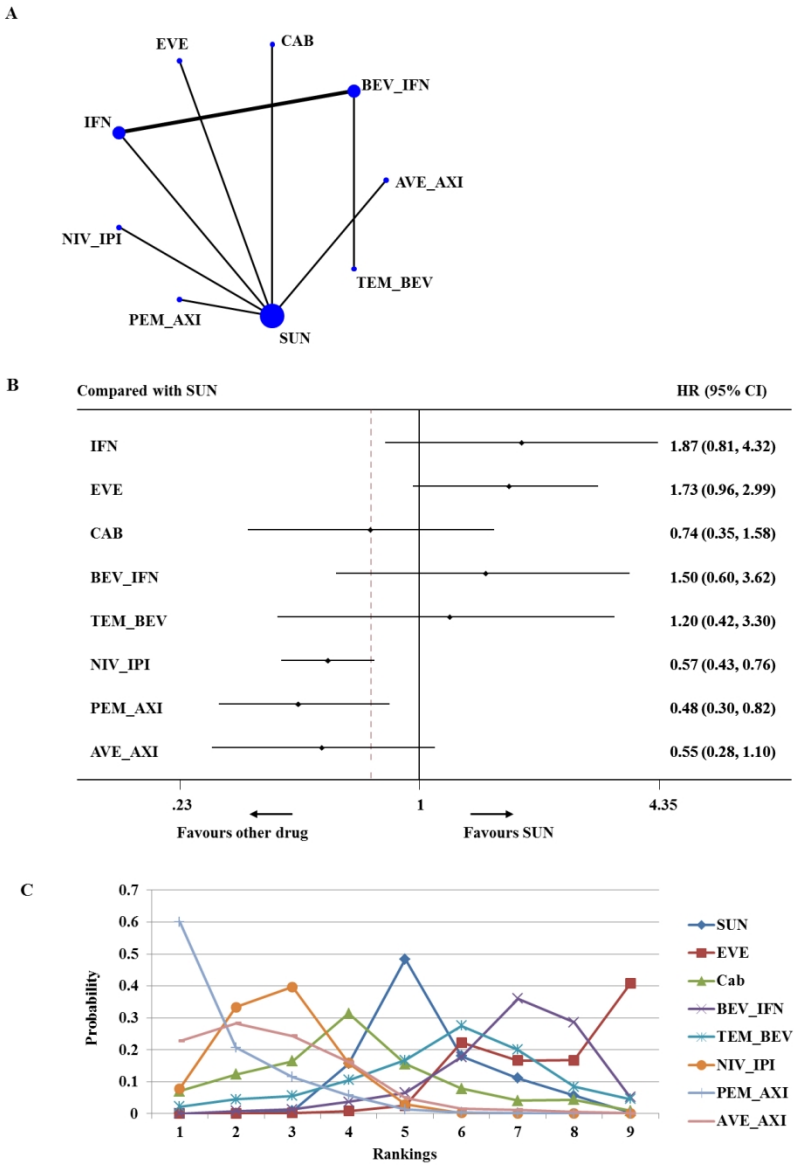


Fig. 4 - Analysis of progression-free survival for patients with poor-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon-α. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

221x322mm (150 x 150 DPI)

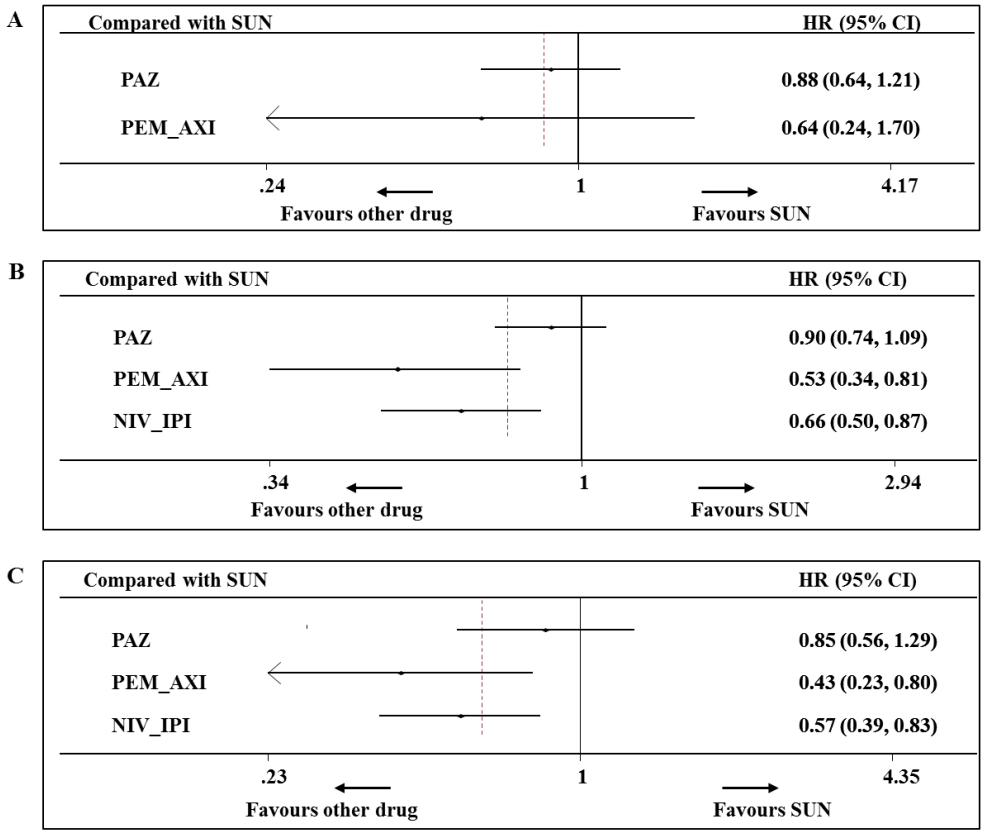


Fig.5- Analysis of overall survival for patients with favorable- risk (A), intermediate- risk (B), and poor-risk (C). HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib.

205x173mm (150 x 150 DPI)

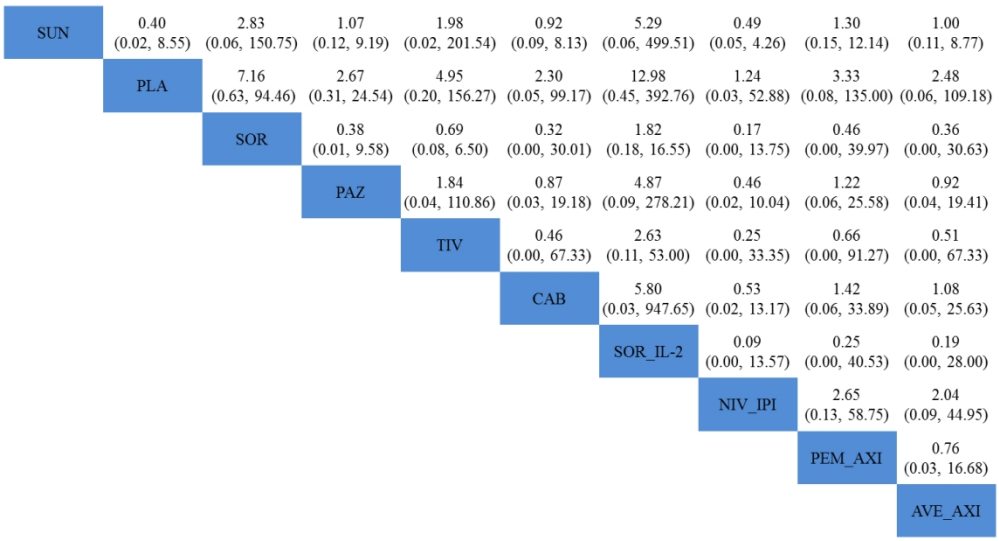


Fig. 6 - Pooled odds ratios for high-grade adverse events.
The column treatment is compared with the row treatment. Odds ratios lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib. Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

256x138mm (150 x 150 DPI)

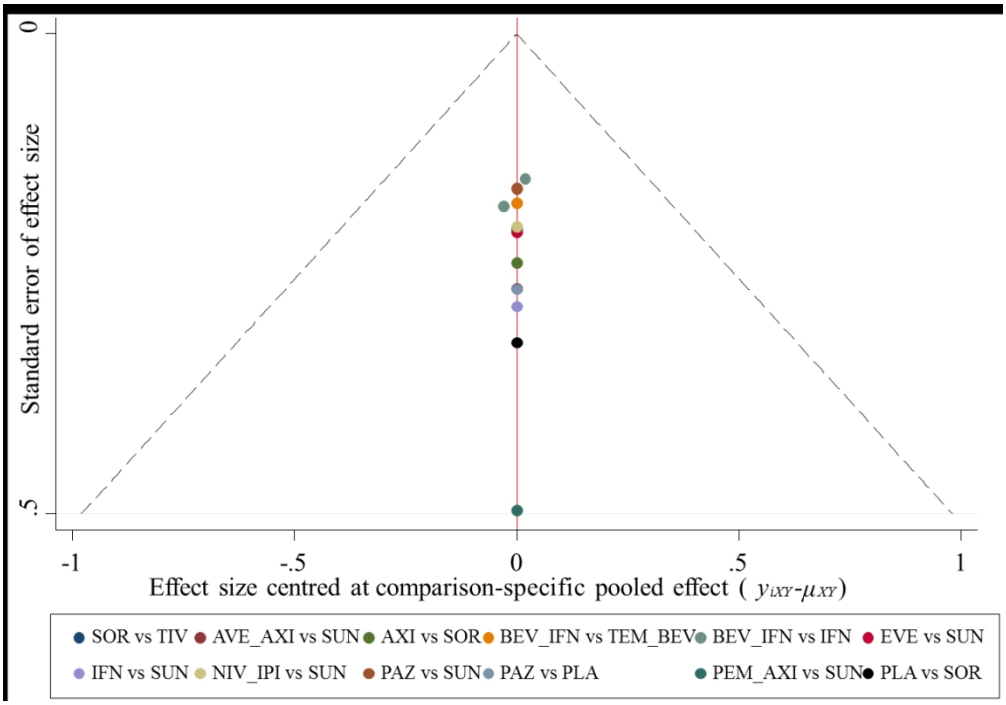


Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis for hazard ratios of progression-free survival

SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

215x150mm (150 x 150 DPI)

Appendix

Search strategy

Pubmed:

((((((((((((sorafenib[Title/Abstract]) OR sunitinib[Title/Abstract]) OR bevacizumab[Title/Abstract]) OR pazopanib[Title/Abstract]) OR temsirolimus[Title/Abstract]) OR everolimus[Title/Abstract]) OR axitinib[Title/Abstract]) OR Cabozantinib[Title/Abstract]) OR IFN-alpha[Title/Abstract]) OR IL-2[Title/Abstract]) OR Nivolumab[Title/Abstract]) OR Immune checkpoint blockade[Title/Abstract])) AND (("Carcinoma, Renal Cell"[Mesh]) OR ((((renal cancer[Title]) OR renal carcinoma[Title]) OR kidney cancer[Title]) OR kidney carcinoma[Title]))
Filter: Controlled Clinical Trial

Cochrane Library:

#1 sorafenib:ti,ab,kw or sunitinib:ti,ab,kw or bevacizumab:ti,ab,kw or temsirolimus:ti,ab,kw or pazopanib:ti,ab,kw (Word variations have been searched)

#2 everolimus:ti,ab,kw or afatinib:ti,ab,kw or cabozanitinb:ti,ab,kw or IFN:ti,ab,kw or IL-2:ti,ab,kw (Word variations have been searched)

#3 nivolumab:ti,ab,kw or Immune checkpoint blockade:ti,ab,kw (Word variations have been searched)

#4 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees

#5 #1 or #2 or #3

#6 #4 and #5, Filter: Trials

Web of science

1 ((((((((((Topic: (sorafenib) OR Topic: (sunitinib)) OR Topic: (bevacizumab)) OR Topic: (pazopanib)) OR Topic: (temsirolimus)) OR Topic: (everolimus)) OR Topic: (afatinib)) OR Topic: (cabozanitinb)) OR Topic: (IFN)) OR Topic: (IL-2)) OR Topic: (nivolumab)) OR Topic: (Immune checkpoint blockade))

2 Title: (renal cell carcinoma) OR Title: (renal cancer) OR Title: (renal carcinoma) OR Title: (kidney cancer) OR Title: (kidney carcinoma)

3 #2 AND #1

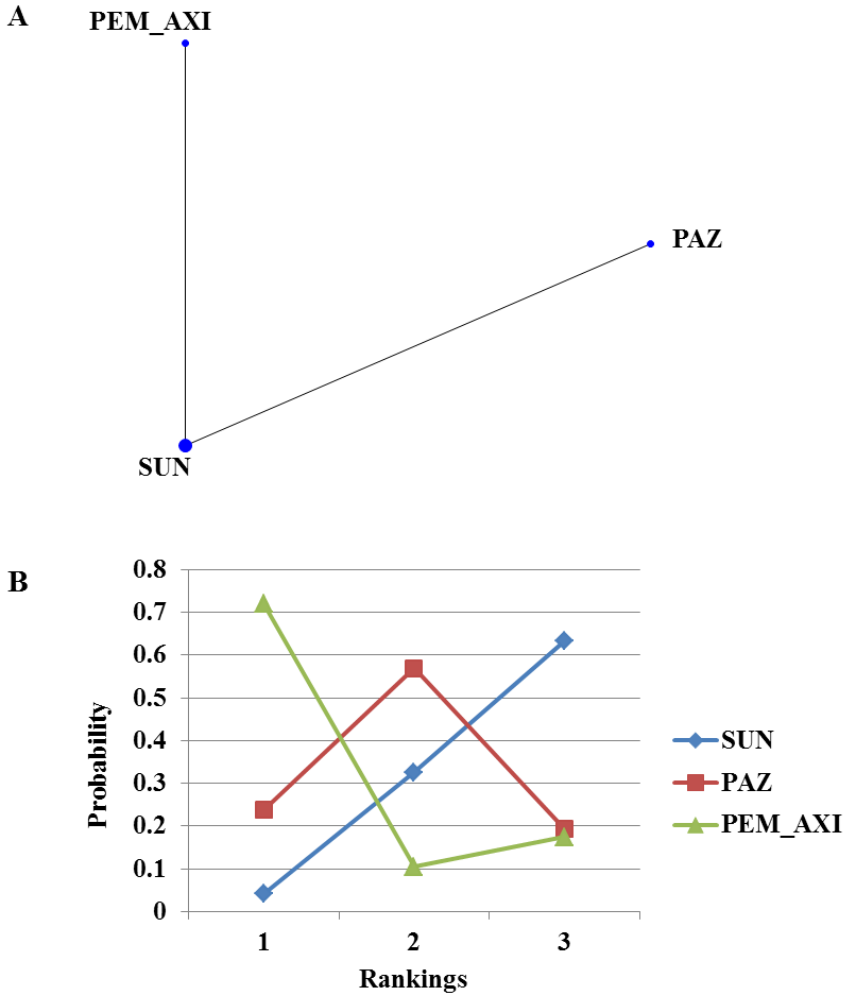
4 #2 AND #1 Document Types: CLINICAL TRIAL

ClinicalTrials.gov:

Category: “renal cell carcinoma OR renal cancer OR renal carcinoma OR kidney cancer OR kidney carcinoma, Studies With Results”

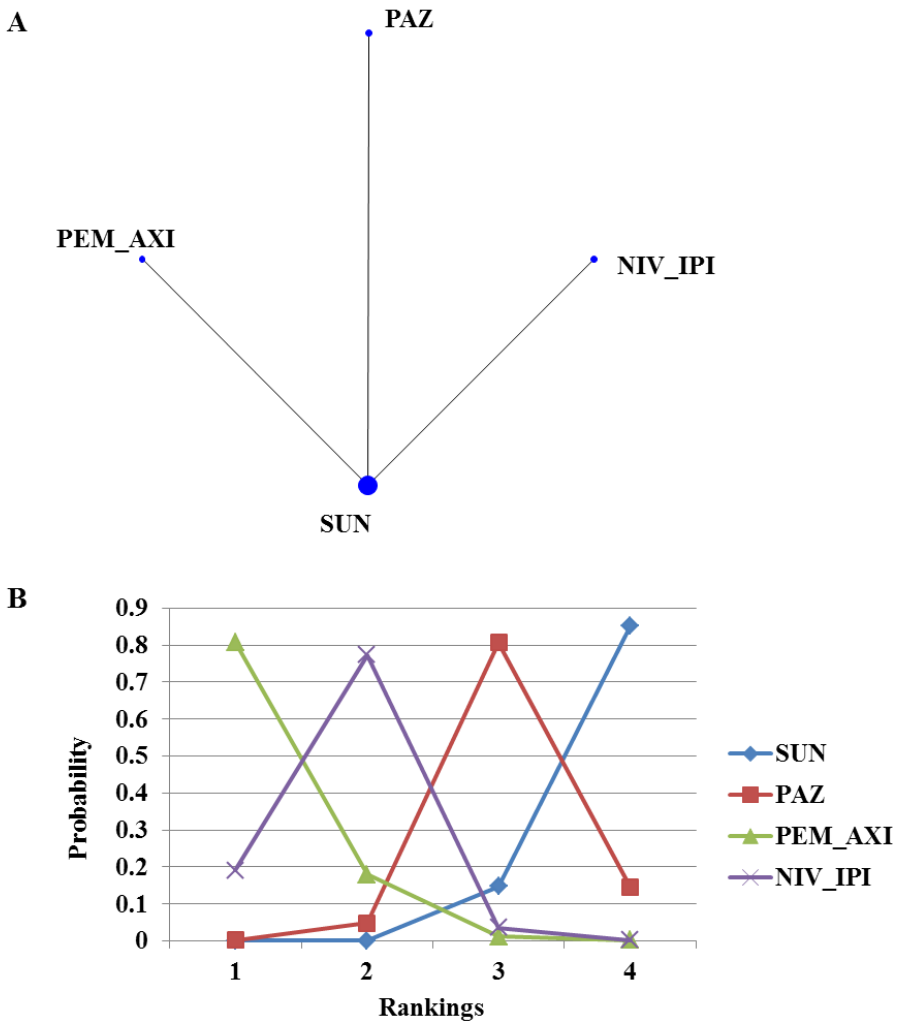
(http://clinicaltrials.gov/)

Appendix figure 1 Analysis of overall survival for patients with favorable-risk disease.



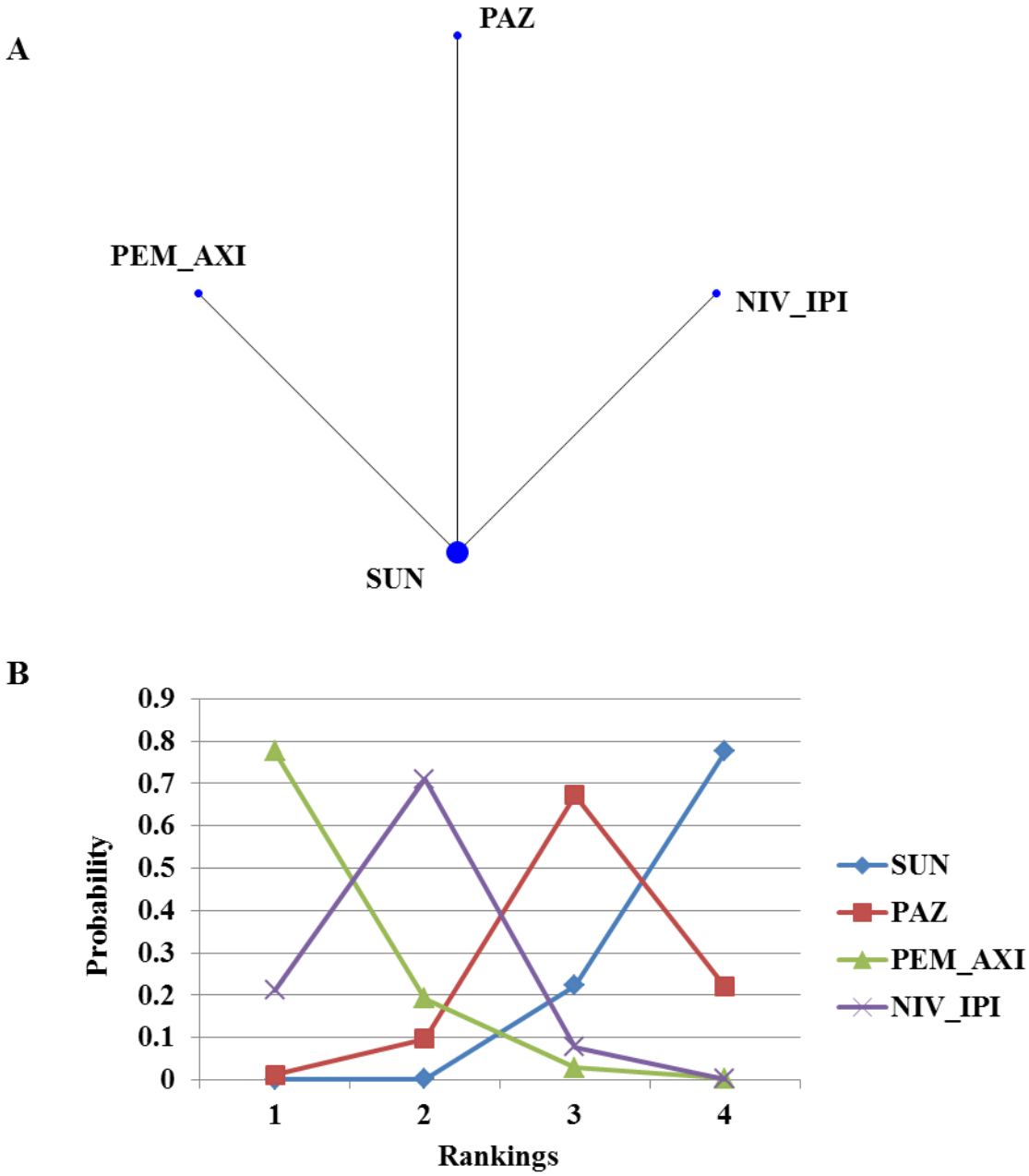
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the three treatments.SUN = sunitinib. PAZ = pazopanib. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 2 Analysis of overall survival for patients with intermediate-risk disease.



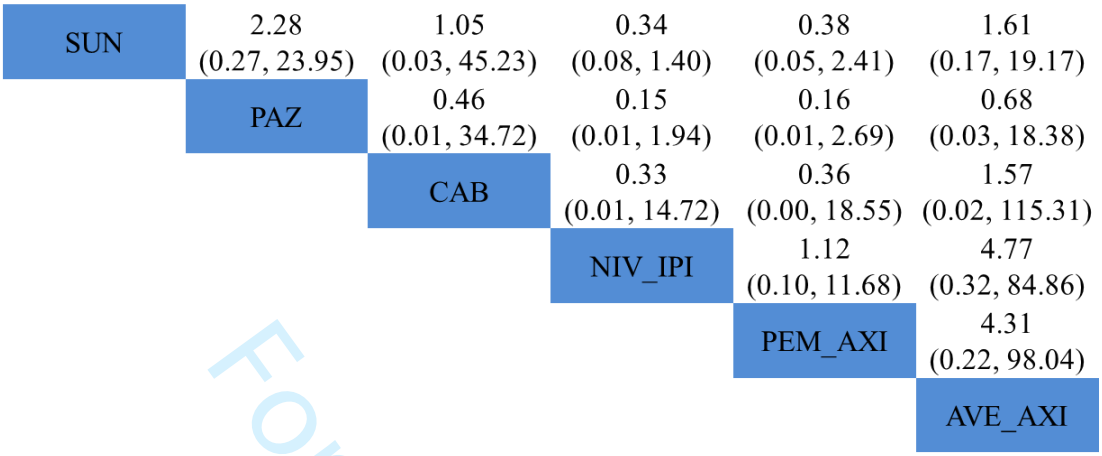
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the four treatments.SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 3 Analysis of overall survival for patients with poor-risk disease.



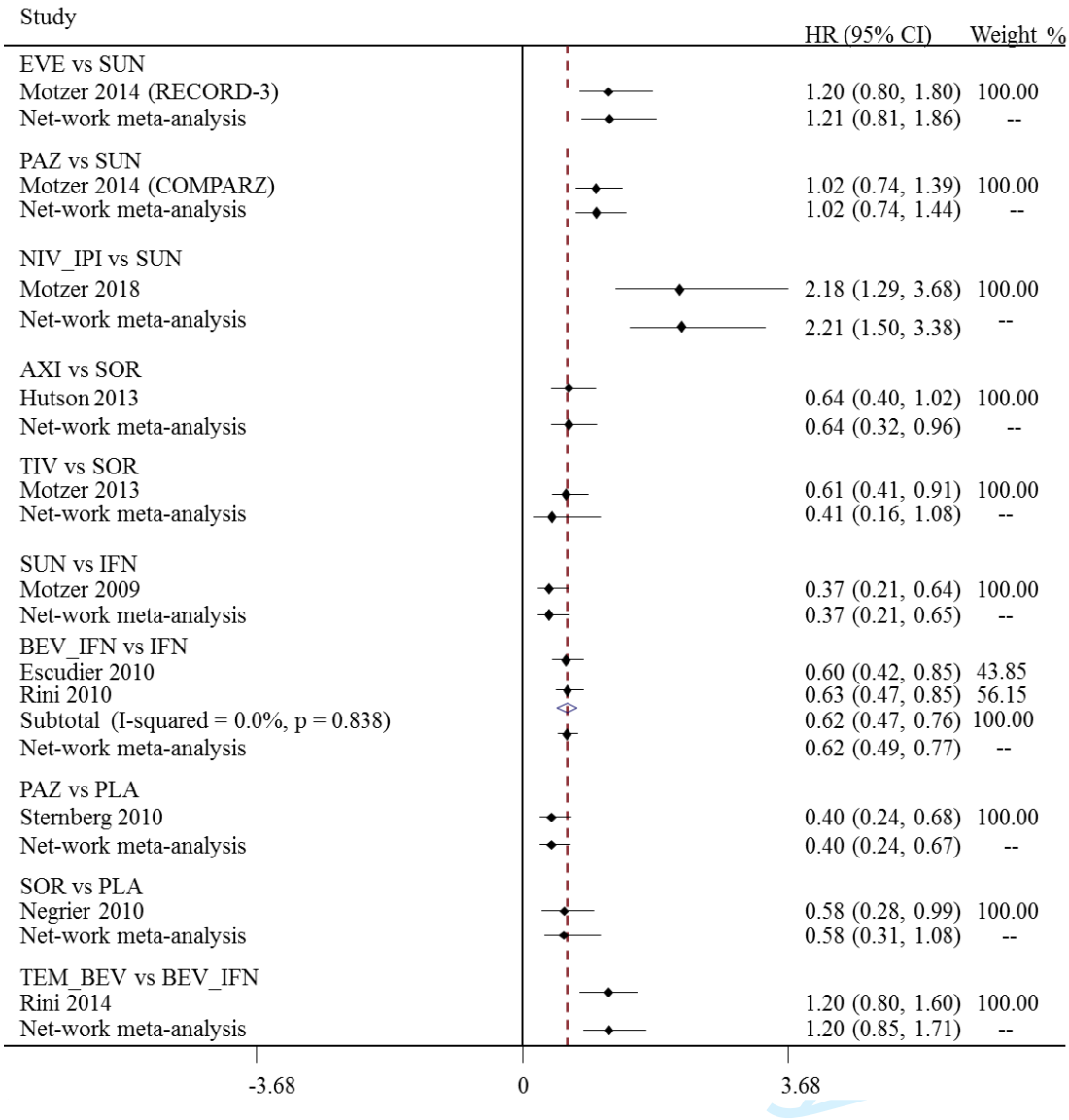
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among the four treatments.SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib.

Appendix figure 4: Pooled odds ratios for **overall adverse events** by Bayesian network meta-analysis



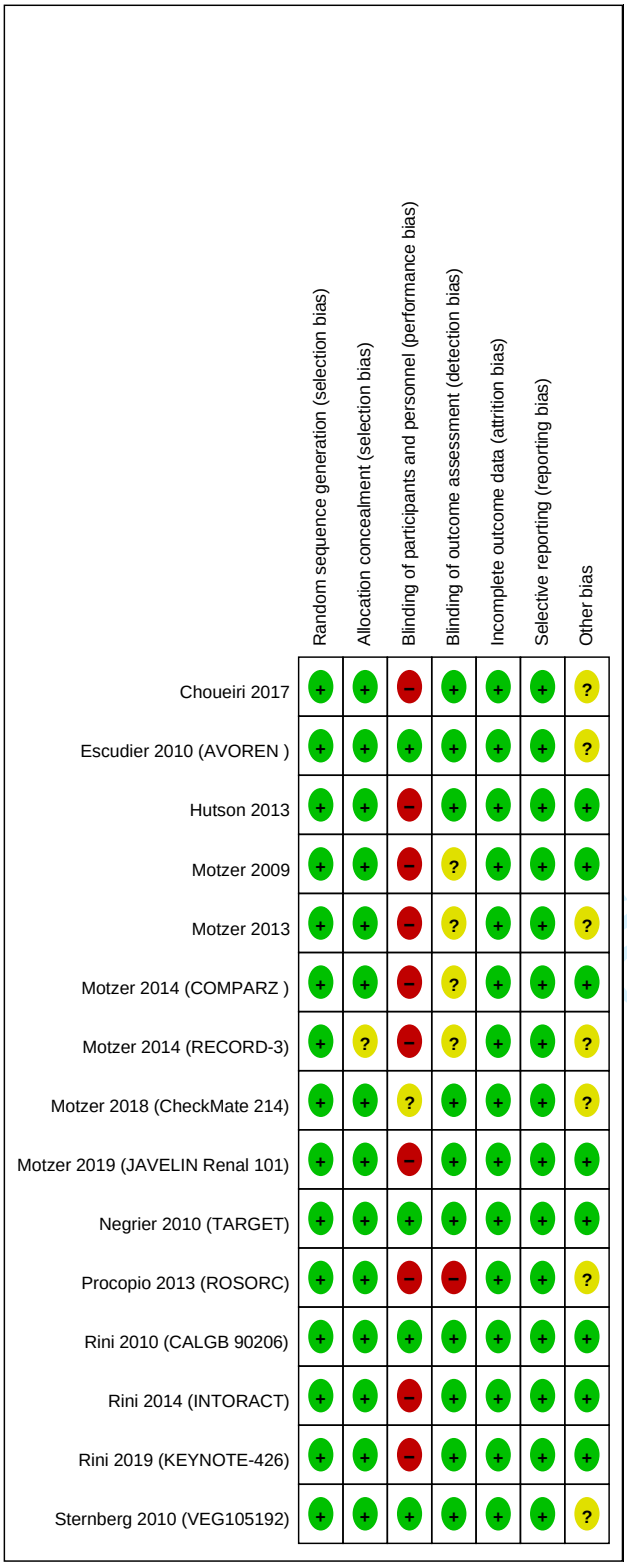
The column treatment is compared with the row treatment. ORs lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. Stepwise comparison of treatments did not find significant differences in rates of overall adverse events. SUN = sunitinib. PAZ = pazopanib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib.

Appendix figure 5 Pooled hazard ratios for progression-free survival by Bayesian network-analysis and traditional meta-analysis



HR = hazard ratio. CI=confidence interval for traditional meta-analysis and credible interval for Bayesian network meta-analysis. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab.

Appendix figure 6 Cochrane risk of bias tool assessment



Appendix Table 1: For advanced/metastatic RCC of favorable-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
PLA	**2.54 (1.37- 4.70)**	2.79 (0.005-4812)
IFN	**2.69 (1.54-4.67)**	2.57 (0.05-18.24)
SOR	1.47 (0.61-3.49)	1.56 (0.001-2735)
PAZ	1.02 (0.74-1.39)	1.03 (0.05-142.4)
AXI	0.93 (0.33-2.54)	0.95 (0.001-22200)
EVE	1.20 (0.80-1.80)	1.28 (0.03-66.05)
BEV_IFN	1.65 (0.90 -2.99)	1.54 (0.01-24.08)
TEM_BEV	1.98 (0.98 -3.96)	1.92 (0.02-155.90)
TIV	0.89 (0.34-2.35)	0.96 (0.001-11940)
NIV_IPI	**2.18 (1.47-3.25)**	2.16 (0.05-52.46)
PEM_AXI	0.64 (0.24-1.69)	0.64 (0.01-64.60)
AVE_AXI	**0.57 (0.34-0.96)**	0.57 (0.01-33.4)
DIC	9.68	11.19

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 2: For advanced/metastatic RCC of intermediate-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
PLA	**1.99 (1.29-3.14)**	2.00 (0.01-1366)
IFN	**2.57 (1.88-3.54)**	2.56 (0.02-283)
SOR	0.95 (0.47-1.91)	0.95 (0.002- 5382)
PAZ	0.98 (0.80-1.18)	0.98 (0.02- 94.94)
AXI	0.80 (0.36-1.81)	0.80 (0.001- 7618)
EVE	**1.50 (1.11-2.01)**	1.50 (0.02-121.20)
CAB	**0.63 (0.44-0.97)**	0.65 (0.01- 64.02)
BEV_IFN	**1.69 (1.18-2.41)**	1.60 (0.01- 895.10)
TEM_BEV	**1.88 (1.22-2.81)**	1.81 (0.002- 4299)
TIV	0.76 (0.36-1.65)	0.79 (0.001- 15210)
NIV_IPI	**0.66 (0.53-0.81)**	0.67 (0.01- 64.51)
PEM_AXI	**0.52 (0.35-0.81)**	0.52 (0.02-10.67)
AVE_AXI	**0.62 (0.47-0.83)**	0.60 (0.02-10.67)
DIC	1.97	2.92

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 3: For advanced/metastatic RCC of poor-risk, comparison of hazard ratios (95% CI) for **progression-free survival** from fixed and random models.

Treatment compared with SUN	Fixed Model	Random Model
IFN	1.87 (0.81- 4.32)	1.88 (0.03- 137.70)
EVE	1.73 (0.96- 2.99)	1.68 (0.02- 89.46)
CAB	0.74 (0.35-1.58)	0.75 (0.01- 54.64)
BEV_IFN	1.50 (0.60-3.62)	1.50 (0.01- 344.20)
TEM_BEV	1.20 (0.42-3.30)	1.22 (0.001- 1196)
NIV_IPI	**0.57 (0.43-0.76)**	0.57 (0.01- 36.17)
PEM_AXI	**0.43 (0.23-0.80)**	0.44 (0.01-53.85)
AVE_AXI	**0.55 (0.28-1.10)**	0.55 (0.01-43.91)
DIC	9.91	11.42

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. IFN = interferon-α. EVE = everolimus. CAB = cabozantinib. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Bold type font indicates significant values.

Appendix Table 4: Comparison of odds ratios (95% CI) for **high-grade adverse event** from consistency and inconsistency models.

Treatment compared with SUN	Consistency Model	Inconsistency Model
PLA	0.40 (0.02, 8.55)	0.39 (0.02, 8.91)
SOR	2.83 (0.06, 150.75)	2.65 (0.05, 160.98)
PAZ	1.07 (0.12, 9.19)	1.05 (0.12, 9.74)
TIV	1.98 (0.02, 201.54)	1.85 (0.02, 209.34)
CAB	0.92 (0.09, 8.13)	0.95 (0.09, 9.10)
SOR_IL-2	5.29 (0.06, 499.51)	4.89 (0.05, 495.91)
NIV_IPI	0.49 (0.05, 4.26)	0.50 (0.06, 4.41)
	1.30 (0.15, 12.14)	1.30 (0.15, 13.03)
	1.00 (0.11, 8.77)	0.98 (0.11, 8.56)
Random Effects Standard Deviation	0.85 (0.07, 1.69)	0.85 (0.07, 1.70)
Inconsistency Standard Deviation	NA	0.87 (0.04, 1.70)

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib.Stepwise comparison of treatments did not find significant differences in rates of high-grade adverse events.

Appendix Table 5: Comparison of odds ratios (95% CI) for **overall-grade adverse event** from consistency and inconsistency models.

Treatment compared with SUN	Consistency Model	Inconsistency Model
PAZ	2.28 (0.27, 23.95)	2.25 (0.30, 24.19)
CAB	1.05 (0.03, 45.23)	1.14 (0.03, 61.85)
NIV_IPI	0.34 (0.08, 1.40)	0.33 (0.08, 1.37)
PEM_AXI	0.38 (0.05, 2.41)	0.41 (0.06, 2.56)
AVE_AXI	1.61 (0.17, 19.17)	1.60 (0.15, 18.66)
Random Effects Standard Deviation	0.52 (0.04, 1.03)	0.53 (0.04, 1.02)
Inconsistency Standard Deviation	NA	0.53 (0.02, 1.02)

Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab, PEM_AXI = pembrolizumab and axitinib, AVE_AXI= avelumab plus axitinib. Stepwise comparison of treatments did not find significant differences in rates of overall-grade adverse events.

Appendix Table 6: Comparison of results from primary analysis and sensitivity analysis for trials assessing approved targeted drugs.

Treatment	Primary Analysis PFS HR (95% CI) vs SUN	Sensitivity Analysis PFS HR (95% CI) vs SUN
PLA	**2.63 (1.47-4.71)**	**2.55 (1.38 -4.66)**
IFN	**2.70 (1.59-4.51)**	**2.71 (1.55 -4.71)**
SOR	1.47 (0.61-3.59)	1.48 (0.62 -3.55)
PAZ	1.03 (0.74-1.44)	1.02 (0.75 -1.41)
AXI	0.98 (0.36-2.76)	0.95 (0.35 -2.54)
EVE	1.21 (0.81-1.86)	1.20 (0.80-1.80)
BEV_IFN	1.66 (0.94 -2.88)	1.67 (0.92 -3.07)
TEM_BEV	**1.96 (1.04 -3.63)**	**2.00 (1.01 -4.03)**
TIV	0.92 (0.37-2.33)	**NA**
NIV_IPI	**2.21 (1.50-3.38)**	**2.18 (1.46-3.20)**

HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PLA = placebo. IFN = interferon-α. SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. BEV_IFN = bevacizumab plus interferon-α. TEM_BEV = temsirolimus plus bevacizumab. TIV = tivozanib. NIV_IPI = nivolumab plus ipilimumab. Bold type font indicates significant values.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.