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

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

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4 head-to-head RCTs to directly investigate the comparative effectiveness of all
5 available therapies. Given the variety of treatment options for patients
6 advanced/metastatic RCC and the limited evidence regarding the optimum treatment
7 strategy, it is a challenge for clinicians to make the best decision.
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11 A previous meta-analysis was attempted to investigate the comparative effects of
12 different systemic agents for treatment of advanced/metastatic RCC [20]. However,
13 trials included in the systematic review enrolled patients with different risk groups.
14 The analysis used aggregate data and did not perform subgroup analysis based on risk
15 strata. In the present study, we performed a Bayesian network meta-analysis to
16 compare first-line systemic treatments for advanced/metastatic RCC of favorable-,
17 intermediate-, and poor-risk, respectively. Network meta-analysis enables indirect
18 comparisons based on a common comparator treatment when a head-to-head trial is
19 unavailable and integrates direct and indirect comparisons to compare several
20 treatment strategies while fully respecting randomization [21, 22]. We aimed to
21 summarize and compare the efficacy and safety associated with currently available
22 systemic therapies for treating advanced/metastatic RCC of different risk categories
23 using network meta-analysis.
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39 **2. Methods**

40 *2.1. Literature-search strategy*

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42 A comprehensive literature search was performed in Pubmed, Web of Science,
43 ClinicalTrials.gov, and Cochrane databases for RCTs of systemic therapies of
44 advanced/metastatic RCC (appendix for all search terms). All the reference lists of
45 identified trials and related reviews were examined to find potential trials. The search
46 was conducted in September 2019. There were no publication date or language
47 restrictions.
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56 *2.2. Inclusion and exclusion criteria*

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58 All studies were selected according to the search strategy based on Preferred
59 Reporting Items for Systematic Reviews and Meta-analyses criteria[23]. Studies were
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4 included if they satisfied three criteria: (1) the study enrolled patients who had
5 histologically or cytologically confirmed advanced/metastatic RCC of favorable-,
6 intermediate-, or poor-risk; (2) patients were randomly assigned to receive systemic
7 therapies alone or in combination. Relevant interventions included, but were not
8 restricted to: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab, ipilimumab,
9 axitinib, tivozanib, everolimus, temsirolimus, bevacizumab, IFN- α or IL-2. Previous
10 systemic therapy for advanced/metastatic RCC was not allowed; (3) one or more of
11 the outcomes of interest mentioned below were reported. Nonoriginal articles,
12 duplicate reports and non-RCTs were excluded.
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23 *2.3. Data Extraction and Quality Assessment*

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25 Two researchers (GH. Cao and XQ. Wu) examined the manuscripts of included
26 trials independently, and extracted data into a structured form, including patient
27 characteristics, treatment strategies, and interest outcomes [PFS, high-grade (grade
28 ≥ 3) and overall drug-related adverse events]. Data were extracted from
29 intention-to-treat analyses as far as possible. The methodological quality of included
30 RCTs was assessed using the Cochrane risk of bias assessment tool [24].
31 Disagreement between investigators was resolved by consensus.
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41 *2.4. Data synthesis and analysis*

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43 First, we performed traditional meta-analyses to compare the treatments using Stata
44 v.12 (StataCorp, College Station, TX, USA). We applied the chi-square test and the I^2
45 statistic to investigate the possibility of heterogeneity among studies. A P value < 0.10
46 or an $I^2 > 50\%$ suggested the presence of substantial heterogeneity.
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51 Second, we did Bayesian network meta-analyses. For meta-analysis of PFS, the
52 reported adjusted hazard ratios (HRs) with 95% CIs were applied as the outcome
53 measure. For studies not reporting HRs, we calculated them employing the pragmatic
54 approach reported by Tierney et al [25]. For drug-related adverse events, we
55 calculated odds ratios (ORs) of every trial for meta-analysis. Both random-effects and
56 fixed-effects models were performed for the analyses [26]. Goodness of model fit was
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4 assessed using the deviance information criterion and between-study standard
5 deviation [26, 27]. Convergence was determined graphically according to the method
6 described by Gelman *et al* [28].
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10 It is believed that certain systemic treatments are effective in certain risk groups
11 than others, for example sunitinib is more effective in favorable-risk patients and
12 nivolumab plus ipilimumab is more effective in intermediate and poor-risk patients
13 [29], suggesting that there is a treatment-by-risk group (favorable-, intermediate-, and
14 poor-risk groups) interaction. Taking no account of this possible interaction in the
15 analysis, we suppose the transitivity assumption across all included trials would be
16 violated. Consequently, we performed all network analyses separately by risk groups
17 (favorable-, intermediate-, and poor-risk groups) according to the MSKCC risk
18 model .
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27 One key assumption for network analysis is that direct and indirect comparisons do
28 not disagree beyond chance [26, 30, 31]. To explore for evidence of inconsistency in
29 the network, investigators compared the estimated treatment effects from the entire
30 network with traditional pair-wise estimates [31]. Sensitivity analyses were performed
31 restricted to trials that assessed approved systemic therapies. Publication bias and
32 small-study effects were assessed using funnel plots [32].
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39 We performed the Bayesian network analysis using OpenBUGS version 3.2.2 for
40 PFS, and Gemtc version 0.14.3 (van Valkenhoef *et al*, 2012) for adverse events. For
41 PFS, we applied 15 000 iterations obtained after a training phase of 10 000-iteration.
42 In order to minimize autocorrelation, we applied a thinning interval of 50 for each
43 chain. For adverse events, we applied the 60 000 iterations after a training phase of 40
44 000 iterations.
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52 **3. Results**

53 *3.1. Search results and study characteristics*

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55 The literature search yielded 1 733 potentially eligible studies, of which 1 625 were
56 excluded based on screening titles and abstracts (Fig. 1). The full text of 108
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4 remaining studies were analyzed, and finally 19 publications reporting 13 unique
5 RCTs were included (Table), involving 7 248 participants randomly assigned to one
6 of the 11 treatment strategies: sorafenib, sunitinib, pazopanib, cabozantinib,
7 nivolumab plus ipilimumab, axitinib, tivozanib, everolimus, IFN- α , bevacizumab plus
8 IFN- α , and temsirolimus plus bevacizumab. According to the MSKCC criteria, there
9 were 2 318, 4 413 and 517 participants had favorable-, intermediate-, and poor-risk
10 disease, respectively.
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17 The main characteristics of included RCTs are summarized in Table. The
18 demographic characteristics of patients were well balanced across trials. Enrolled
19 patients across trials were similar in terms of age, gender, and risk classification.
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21 Across trials, the median age of patients ranged from 58 to 64 years. The participants
22 were predominantly male (71%, 5 163 of 7 248). The included trials were designed
23 similarly. Median follow-up ranged from 18.75 to 58 months. The mean sample sizes
24 were 105, 184 and 37 patients per group for favorable-, intermediate- and poor-risk
25 subtypes, respectively. 11 trials selected for clear-cell carcinoma subtypes [8-10, 14,
26 15, 33-38], and two trials also included small subsets of non-clear-cell histotypes,
27 each comprising 11% and 14% of the study population, respectively [39, 40]. All
28 studies were two-arm trials. The dosages used in most of trials were within the
29 recommended dose ranges.
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40 In this network meta-analysis, results are reported based on fixed-effects models
41 because they demonstrated better goodness of fit compared with random-effects
42 models. The results of random-effects models are available in appendix Table 1-5.
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48 *3.2. Progression-free survival*

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50 *3.2.1.* For advanced/metastatic RCC of favorable-risk, 11 trials enrolling 2 318 total
51 patients reported adequate information on progression-free survival and contributed to
52 network meta-analysis (Fig. 2A) [8-11, 14, 15, 34-37, 39, 40]. Fig. 2B summarises the
53 results of the network meta-analysis for PFS. Compared with sunitinib, IFN- α ,
54 temsirolimus plus bevacizumab, and nivolumab plus ipilimumab were associated with
55 significantly worse PFS (HR 2.70, 95% CI 1.59-4.51; HR 1.96, 95% CI 1.04-3.63;
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4 and HR 1.56, 95% CI 1.32-1.84, respectively). Based on the analysis of SUCRA,
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6 there was a 41.7% chance that sunitinib provided the greatest PFS benefit for patients
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8 with favorable-risk disease (Fig. 2C).
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11 3.2.2. For advanced/metastatic RCC of intermediate-risk, 12 trials enrolling 4 413
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13 total patients contributed to the analysis of PFS (Fig. 3A) [8-11, 14, 15, 33-37, 40].
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15 Network meta-analysis demonstrated that nivolumab plus ipilimumab and
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17 cabozantinib were associated with significantly higher improvement in PFS than
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19 sunitinib (HR 0.66, 95% CI 0.54-0.81; HR 0.64, 95% CI 0.43-0.96, respectively).
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21 Temsirolimus plus bevacizumab, and bevacizumab plus IFN- α were significantly less
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23 efficacious for PFS than sunitinib (HR 1.85, 95% CI 1.21-2.81; HR 1.68, 95% CI
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25 1.18-2.40) (Fig. 3B). Based on the analysis of SUCRA, cabozantinib was most likely
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27 to be the best treatment for intermediate-risk patients. Nivolumab plus ipilimumab
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29 was likely to be second-best treatment, while axitinib and tivozanib had a similar
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31 likelihood of being the third-best option for patients with intermediate-risk disease
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33 (Fig. 3C).
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37 3.2.3. Based on data that was available for advanced/metastatic RCC of poor-risk, the
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39 network involved seven trials comparing seven different treatments (517 total patients;
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41 Fig. 4A) [14, 15, 33-35, 37, 40]. Network meta-analysis demonstrated that only
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43 nivolumab plus ipilimumab was associated with a significantly higher improvement in
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45 PFS than sunitinib (HR 0.57; 95% CI 0.4-0.70) (Fig. 4B). On SUCRA-based analysis,
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47 there was a 67.7% probability that nivolumab plus ipilimumab had the greatest PFS
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49 for poor-risk patients (Fig. 4C)
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51 52 3.3. *Adverse events* 53

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

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4 in Fig. 5 and appendix Fig. 1 Stepwise comparison of all the seven therapies did not
5 find significant differences in rates of high-grade or overall adverse events.
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9 3.4. Network assumptions, sensitivity analysis, publication bias, and risk of bias

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

29 Our network meta-analysis of 13 RCTs including 7 248 individuals assessed the
30 efficacy and safety of all major systematic therapies for the treatment of
31 advanced/metastatic RCC in the first-line setting. Findings of this meta-analysis might
32 help to choose among systemic agents for the management of patients with previously
33 untreated advanced/metastatic RCC. For advanced/metastatic RCC of favorable-risk,
34 sunitinib was most likely to be the best treatment regimen. For patients with
35 intermediate-risk, cabozantinib seemed to be the most efficacious treatment strategy.
36 For poor-risk patients, nivolumab plus ipilimumab provided obvious PFS advantages
37 over other treatments. In terms of drug-related adverse events, there were no
38 significant differences among systemic therapies.
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50 In RCC with clear cell subtype, hypoxia-inducible factor (HIF) accumulation due to
51 loss of von Hippel-Lindau (VHL) leads to overexpression of VEGF and platelet
52 derived growth factor (PDGF), which promotes tumor angiogenesis [41-43]. This
53 process substantially makes a contribution to the development and progression of
54 clear cell RCC. Inhibiting the VEGF signaling has been supposed as the key
55 mechanism for antitumor effects in clear cell RCC. To date, eight targeted drugs have
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4 been approved for treating advanced RCC: sunitinib, sorafenib, pazopanib,
5 cabozantinib, axitinib, everolimus, temsirolimus, and bevacizumab (in combination
6 with IFN- α).
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9 As shown in this analysis, for patients with intermediate-risk, sunitinib resulted in a
10 significant PFS benefit compared with everolimus. The varied clinical benefit could
11 be associated with mechanisms of action of TKI and mTOR inhibitor. Sunitinib not
12 be associated with mechanisms of action of TKI and mTOR inhibitor. Sunitinib not
13 only inhibit VEGF receptors -1, -2, and -3, which may be the most clearly relevant
14 targets in RCC so far, but also exhibit potent activity against PDGF receptor [9, 44]. It
15 has been reported that PDGF plays a critical role in the recruitment of pericytes to
16 sprouting tumor vessels, and pericyte-covered vessels are more likely resistant to
17 anti-vascular therapy than those pericyte-negative vessels [45, 46]. The mTOR
18 complex is the upstream of an intracellular signaling network regulating cell growth
19 and angiogenesis, and it plays a key role in the pathogenesis of advanced/metastatic
20 RCC [47]. It has been demonstrated that rapamycin analogs, including everolimus and
21 temsirolimus, inhibit only one of two signaling complexes of mTOR [48]. The
22 mTORC1 signaling is potently inhibited by everolimus and temsirolimus, while the
23 mTORC2 signaling is not [49]. Consequently, one downstream signaling of mTOR
24 activation is unopposed. The relatively unsatisfactory efficacy should disable the
25 mTOR inhibitors as more suitable therapies for the treatment of advanced/metastatic
26 RCC than TKIs. Regarding TKIs, our results suggest that sunitinib was most likely
27 to be the best treatment regimen for patients with favorable-risk disease.
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31 A potentially additive benefit from combinations of targeted drugs has been
32 suggested on the basis that they inhibit separate cellular pathways. However, our
33 results show that temsirolimus plus bevacizumab, and bevacizumab plus IFN- α
34 provide little survival benefit compared with sunitinib, further confirming absence of
35 evidence that combination treatment simultaneously inhibiting both VEGF and
36 mTOR signaling results in therapeutic synergy [17, 19, 37, 50, 51].
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40 For patients with intermediate-risk, cabozantinib seemed to be the most efficacious
41 treatment strategies. Our study results show that cabozantinib demonstrates clinical
42 superiority over sunitinib among patients with intermediate-risk. The benefit of
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4 cabozantinib over sunitinib may reflect the target tyrosine kinases of cabozantinib,
5 which includes AXL and MET in addition to VEGF receptors. It is reported that
6 upregulated AXL or MET is closely related to resistance to VEGF receptor inhibitors
7 and poor prognosis in several cancer models [52-55]. Therefore, targeting these two
8 oncoproteins in addition to VEGF receptors may provide further antitumor effects in
9 RCC than more selective VEGF receptors targeted agents.
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15 Immune checkpoint antibodies block the inhibitory T-cell receptor programmed
16 death-1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4)-signaling to augment
17 tumor specific immune response [56]. Nivolumab (an anti-PD-1 antibody) is
18 approved for the treatment of advanced RCC in the second line setting. Ipilimumab
19 (an anti-CTLA-4 antibody) is approved for the treatment of advanced melanoma.
20 Nivolumab plus ipilimumab has been reported significant efficacy in multiple tumor
21 types [57-60].
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29 In this analysis, nivolumab plus ipilimumab was associated with a significant PFS
30 advantage compared with sunitinib among intermediate- and poor-risk patients. In
31 contrast, sunitinib was associated with a significantly longer PFS than nivolumab plus
32 ipilimumab among favorable-risk patients. The inconsistent results of the comparison
33 between nivolumab plus ipilimumab and sunitinib may be explained by different
34 mechanisms of action. It's reported that immunotherapy might be associated with
35 "pseudo-progression" phenomenon according to the (Response Evaluation Criteria in
36 Solid Tumors) RECIST criteria [61, 62]. For instance, in a subgroup analysis of the
37 CheckMate 025 trial comparing nivolumab with everolimus for mRCC in second-line
38 setting, 69% patients treated beyond progression demonstrated sustained tumor
39 reduction or target lesion stabilization [63]. As such, no significant PFS results in
40 immunotherapy clinical trials are understandable, and this different mechanism of
41 action likely explains inconsistent results of nivolumab plus ipilimumab compared
42 with sunitinib. Regardless of the mechanism, these results highlight the need to better
43 understand the biologic mechanisms of different treatment regimens. Combinations of
44 immune therapy with targeted therapy may provide the best opportunity to maximize
45 survival benefit [64].
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4 There are several factors which make an analysis of OS challenging, therefore
5 meta-analysis on OS was not performed. First, the OS data were not reported in five
6 included studies. Second, for the available OS data, there were issues of confounders,
7 such as crossover to more efficacious treatment and the influence of subsequent
8 anticancer therapies [33, 36, 65]. These factors can substantially underestimate the
9 difference between two treatments in terms of OS. In addition, PFS has been
10 recognized as a surrogate endpoint of OS in medical oncology as well as in
11 advanced/metastatic RCC in the TKI era [66].
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19 The strengths of our study are as follows. To the best of our knowledge, this study
20 is the first network analysis to compare systemic treatments for advanced/metastatic
21 RCC separately by risk groups. We applied multiple rigorous search strategies to
22 retrieve all potentially eligible RCTs. In the present study, we comprehensively
23 compared and ranked all available first-line systemic therapies for
24 advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively,
25 thus providing physicians with an overall appraisal of systemic therapies for different
26 risk groups. In addition, we used Bayesian network meta-analysis to synthesize data.
27 This approach provides indirect effect estimates in the absence of head-to-head trial
28 and incorporates all available information from RCTs while fully maintaining
29 randomization [21, 22]. We applied various statistical models to increase reliability of
30 the results. Results were consistent across all analyzed outcomes. Moreover, the
31 reliability and accuracy of results were corroborated by the low statistical
32 heterogeneity and excellent model fit. Finally, assessment of both efficacy and
33 adverse events provides new insights into the benefit-harm balance of different
34 systemic treatments.
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50 However, the limitations of our study must be taken into account. The major
51 limitation of this network meta-analysis lies in the reporting quality of trials reviewed.
52 Eight included trials were not masked, which might affect the validity of our findings.
53 Moreover, this meta-analysis was conducted based on summary statistics rather than
54 individual patient level data. There might be some confounding factors (*e.g.*, ethnic
55 origin, prior nephrectomy, *etc.*) at the individual patient level that might influence the
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4 benefit of systemic treatments, but were not available; therefore analyses adjusted for
5 these factors were impossible in our network meta-analysis. Access to patient-level
6 longitudinal data would allow us to establish more robust and accurate conclusions in
7 specific subgroups of patients. Moreover, the length of follow-up varied across
8 studies, resulting in potential variations in survival benefits of systemic treatments.
9 Due to only five trials reporting median follow-up, sensitivity analyses adjusted for
10 this factor were impossible. Moreover, individual dosage varied across studies and
11 data were too sparse to investigate effects of different schedules, which might
12 somewhat affect the generalisability of our findings. Finally, findings in this
13 meta-analysis were mainly based on patients with clear-cell advanced RCC, thus no
14 robust recommendations can be provided for non-clear-cell subtypes.
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27 **5. Conclusions**

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

- 44 ▶ This is the first network analysis to compare systemic treatments for
45 advanced/metastatic RCC separately by risk groups.
- 46 ▶ Various statistical models were applied to synthesize data. The reliability and
47 accuracy of results were corroborated by the low statistical heterogeneity and
48 excellent model fit.
- 49 ▶ Assessment of both efficacy and adverse events provides new insights into the
50 benefit-harm balance of different systemic treatments.
- 51 ▶ Main limitation lies in the reporting quality of trials included.
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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.

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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.

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

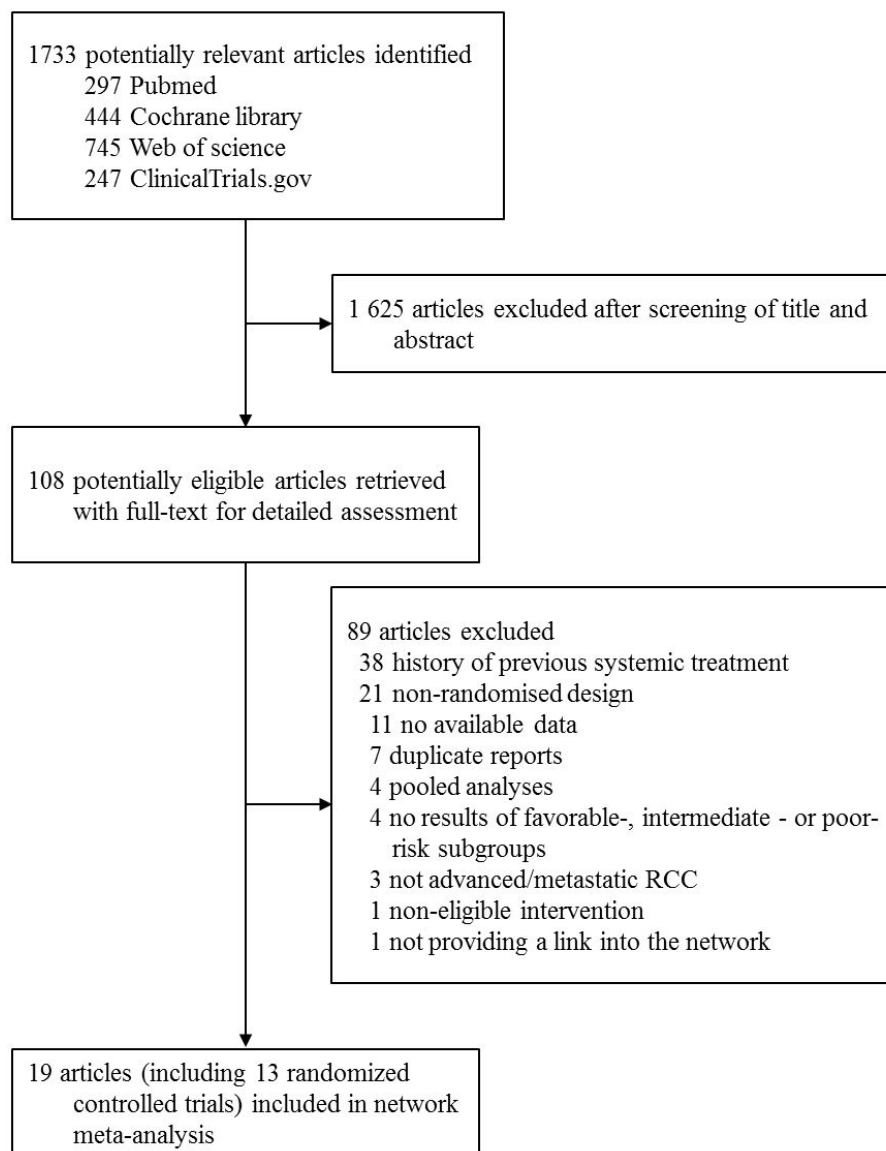
Study	Number of patients	Age (years) median(range)	Sex (% male)	MSKCC (%)			Median PFS in months (95% CI)	Hazard ratio (95% CI)
				Favorable	Intermediate	Poor		
Motzer 2014 (RECORD-3)								
Everolimus	238	62 (20-89)	69.7	29	56	15	7.9	1.4 (1.2-1.8)
Sunitinib	238	62 (29-84)	73.9	30	56	14	10.7	1 (Ref)
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)								
Teniposol 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								
Tibozanib	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)

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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								
Capzantinib	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)

17 IFN- α = interferon- α ; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; CI = confidence interval; AE = adverse event;
 18 NA = not available; Ref = reference group (hence hazard ratio set to 1);
 19 * interquartile range; † mean; ‡ 99.1% CI; § IMDC risk group, International Metastatic Renal Cell Carcinoma Database Consortium
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Figures**Fig. 1 - Literature search and selection**

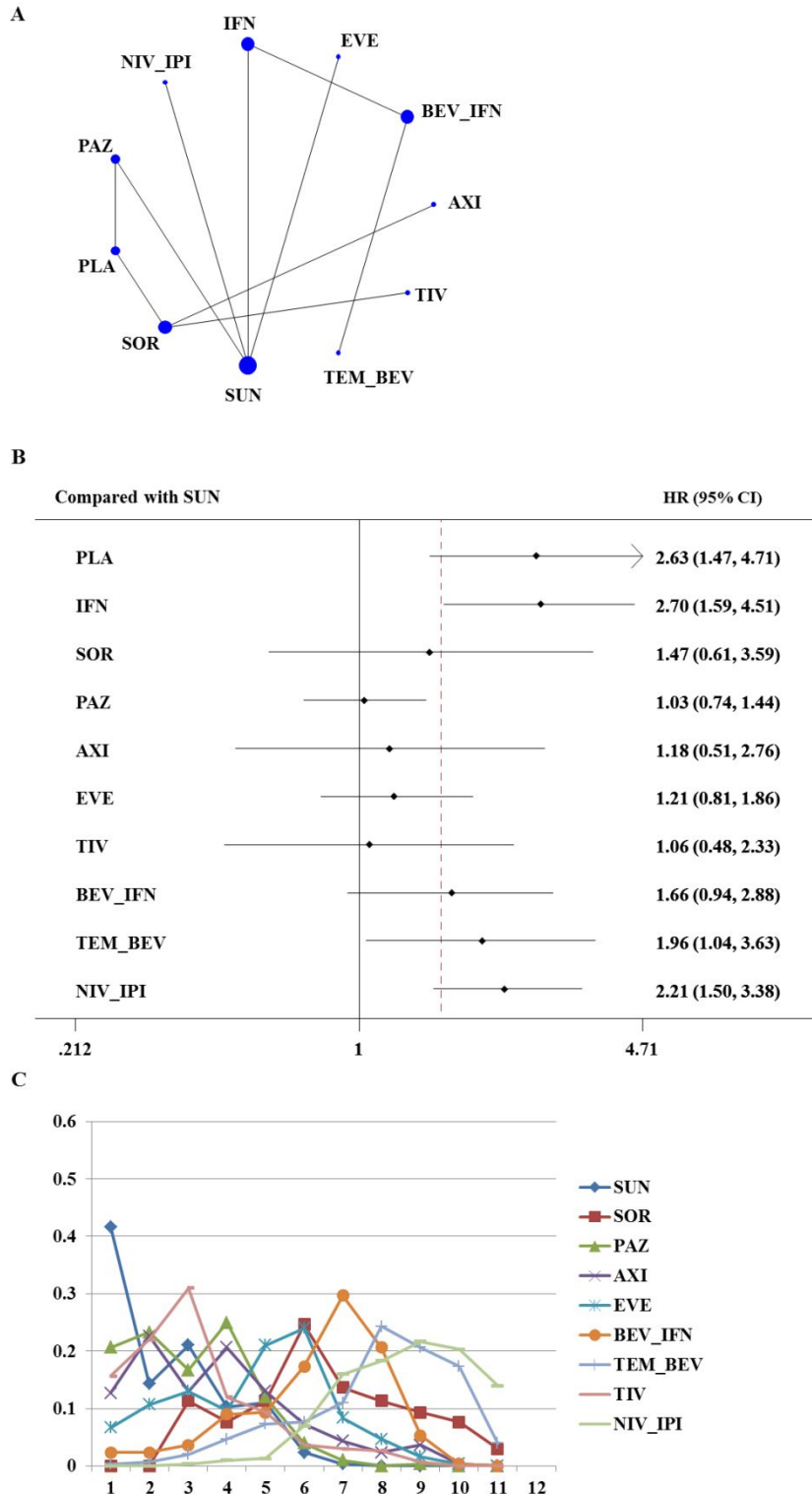


Fig. 2 - Analysis of progression-free survival for patients with favorable-risk disease. (A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) forest plot, with sunitinib as the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

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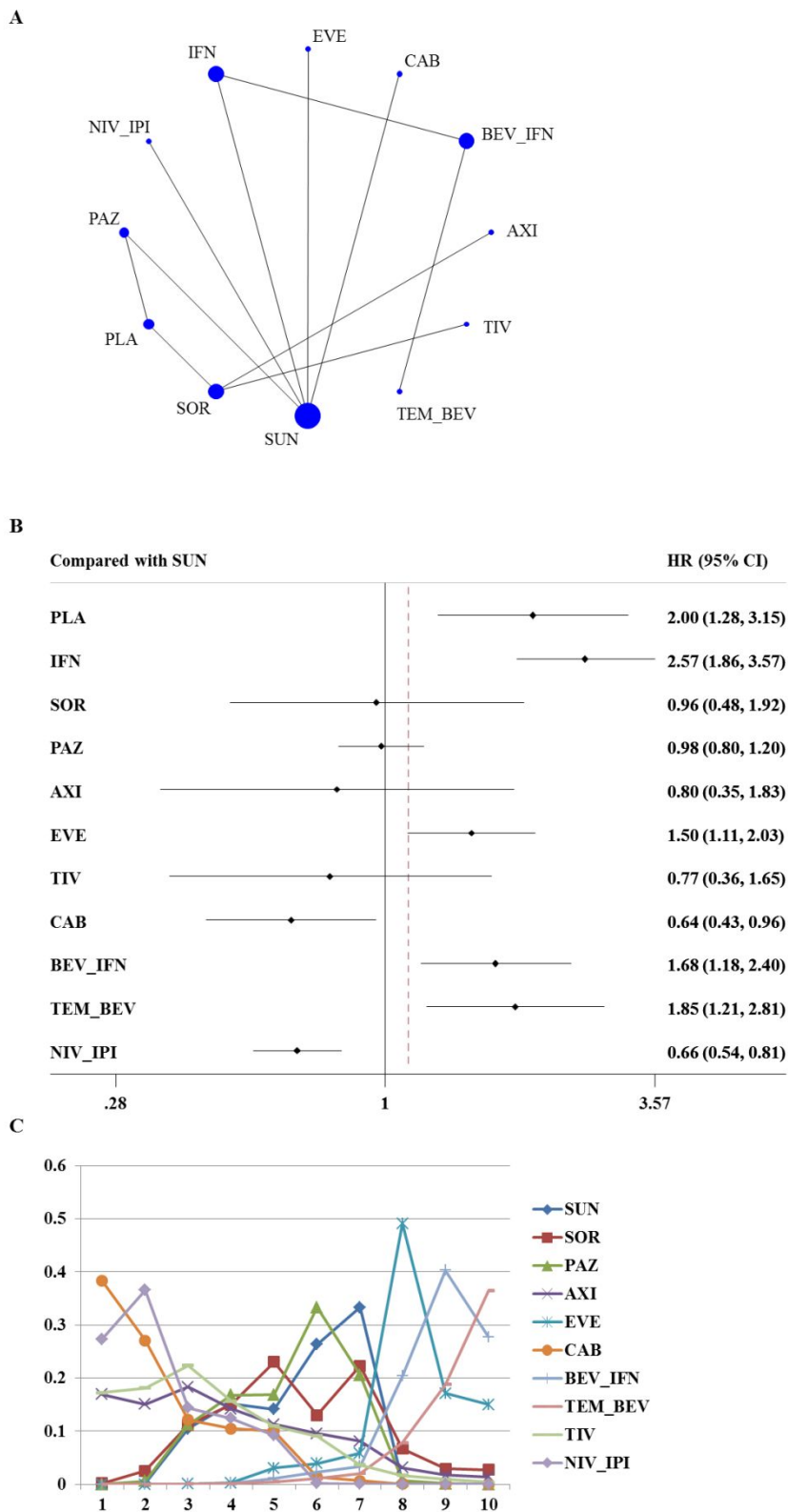


Fig. 3 - Analysis of progression-free survival for patients with intermediate-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C)

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4 SUCRA plot.

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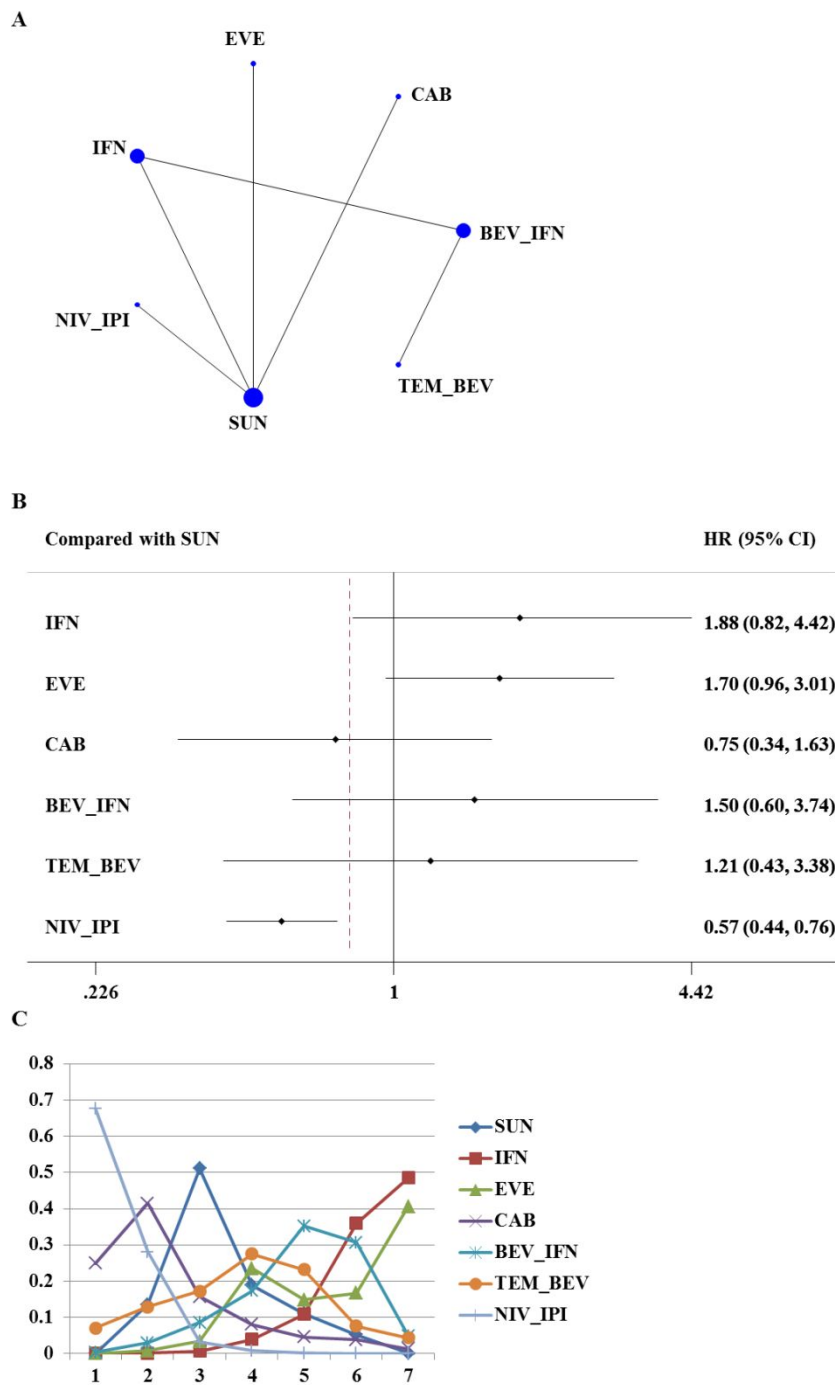


Fig. 4 - Analysis of progression-free survival for patients with poor-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) SUCRA plot.

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.

SUN	0.38 (0.02, 8.57)	2.64 (0.06, 155.18)	1.02 (0.13, 9.41)	1.84 (0.02, 177.32)	0.91 (0.10, 8.90)	4.75 (0.06, 517.51)	0.49 (0.06, 4.59)
	PLA	6.81 (0.67, 90.47)	2.61 (0.31, 23.27)	4.76 (0.19, 130.86)	2.31 (0.05, 101.89)	12.45 (0.50, 408.59)	1.29 (0.03, 56.04)
		SOR	0.39 (0.01, 9.42)	0.67 (0.08, 5.76)	0.37 (0.00, 26.62)	1.75 (0.19, 16.73)	0.19 (0.00, 15.41)
			PAZ	1.75 (0.04, 96.67)	0.87 (0.04, 19.06)	4.53 (0.09, 270.47)	0.49 (0.02, 9.84)
				TIV	0.53 (0.00, 62.41)	2.48 (0.12, 59.27)	0.27 (0.00, 34.46)
					CAB	4.96 (0.04, 907.75)	0.56 (0.02, 12.11)
						SOR_IL-2	0.11 (0.00, 13.36)
							NIV_IPI

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.

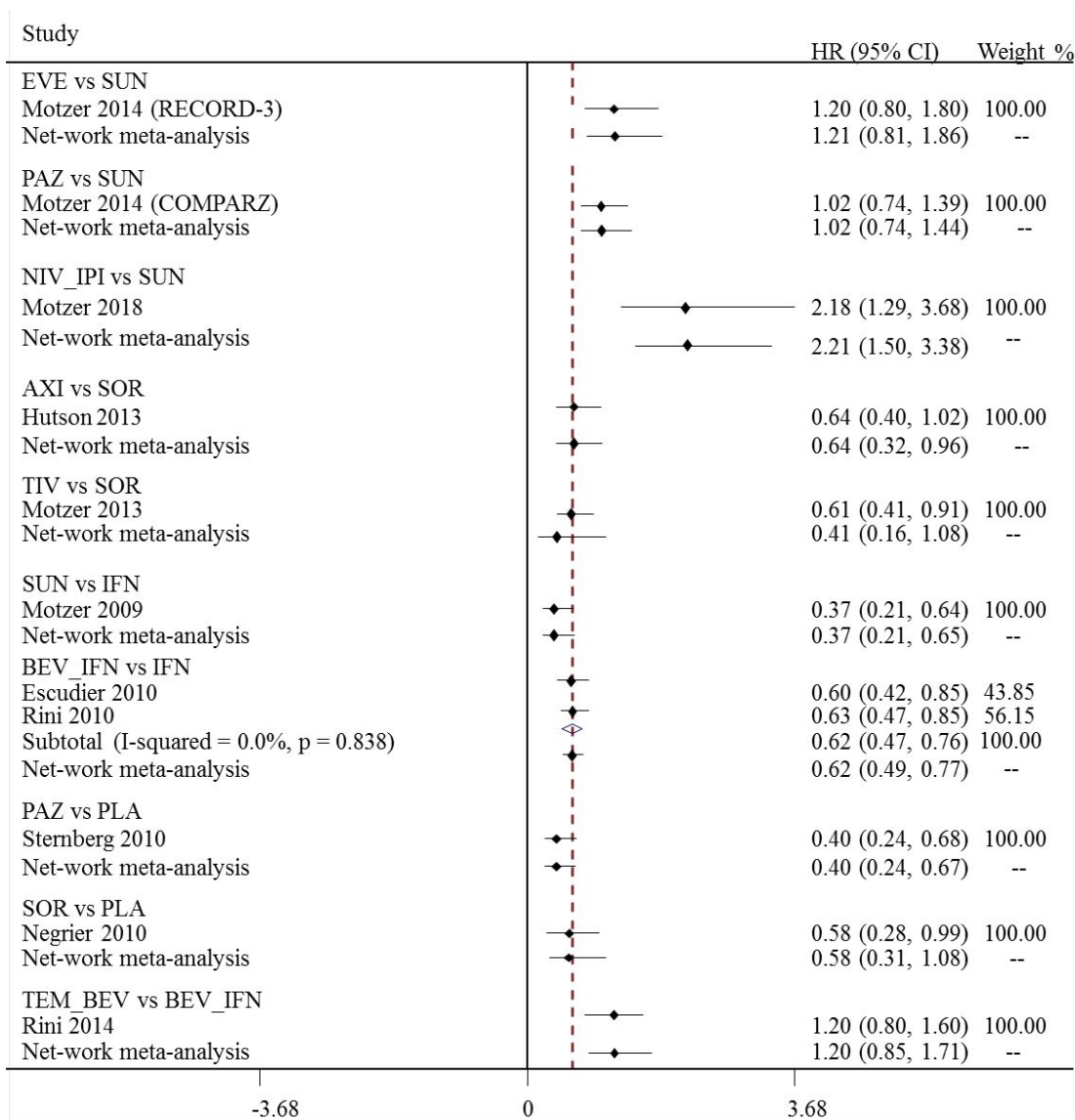


Fig. 6 - Pooled hazard ratios for progression-free survival by Bayesian network-analysis and traditional meta-analysis

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.

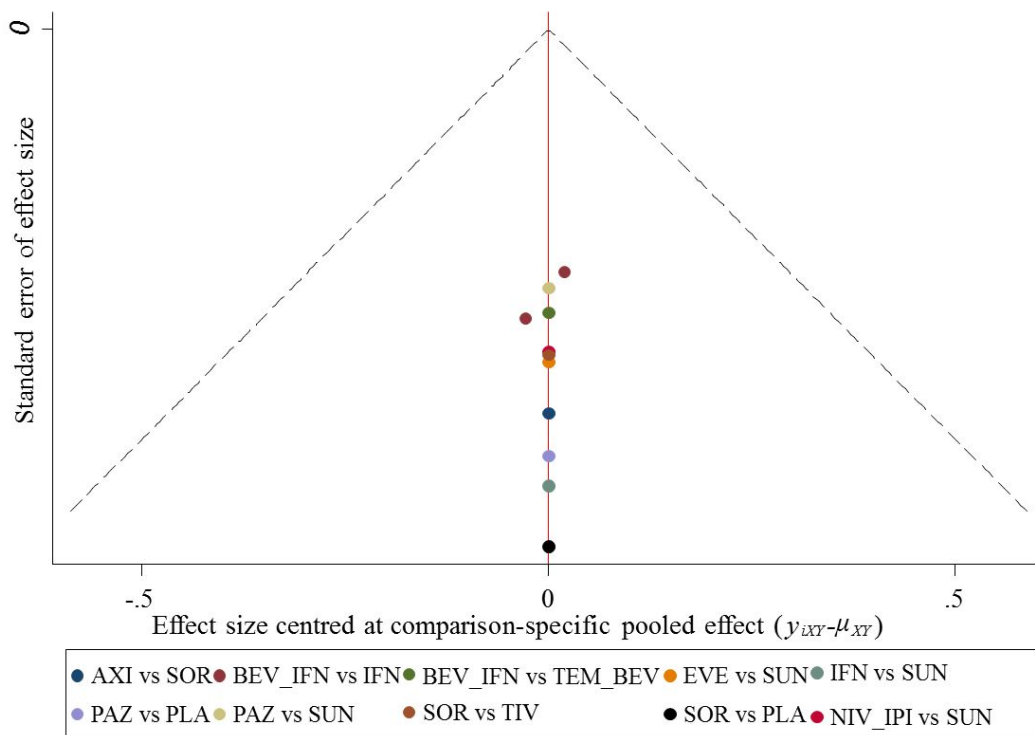


Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis for hazard ratios of progression-free survival

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 cabozantinib: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:
 (cabozantinib)) 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

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4 **ClinicalTrials.gov:**

5 Category: “renal cell carcinoma OR renal cancer OR renal carcinoma OR kidney cancer OR

6 kidney carcinoma, Studies With Results”

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

SUN	2.26 (0.26, 25.07)	1.10 (0.02, 34.61)	0.34 (0.08, 1.38)
	PAZ	0.50 (0.00, 28.54)	0.15 (0.01, 1.90)
		CAB	0.30 (0.01, 20.92)
			NIV_IPI

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Choueiri 2017	+	+	-	+	+	+	?
Escudier 2010 (AVOREN)	+	+	+	+	+	+	?
Hutson 2013	+	+	-	+	+	+	+
Motzer 2009	+	+	-	?	+	+	+
Motzer 2013	+	+	-	?	+	+	?
Motzer 2014 (COMPARZ)	+	+	-	?	+	+	+
Motzer 2014 (RECORD-3)	+	?	-	?	+	+	?
Motzer 2018 (CheckMate 214)	+	+	?	+	+	+	?
Negrier 2010 (TARGET)	+	+	+	+	+	+	+
Procopio 2013 (ROSORC)	+	+	-	-	+	+	?
Rini 2010 (CALGB 90206)	+	+	+	+	+	+	+
Rini 2014 (INTORACT)	+	+	-	+	+	+	+
Sternberg 2010 (VEG105192)	+	+	+	+	+	+	?

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

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology
Keywords:	Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY, IMMUNOLOGY

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4 **What's the optimum systemic treatment for advanced/metastatic**
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6 **renal cell carcinoma of favorable-, intermediate- and poor-risk,**
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8 **respectively? A systematic review and network meta-analysis**
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13 Guanghui Cao, Xiaoqiang Wu, Zhiwei Wang, Xiangyong Tian, Chan Zhang, Xuan Wu, Haotian
14 Zhang, Gaopeng Jing, Tianzhong Yan
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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.

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4
5 **Keywords:** renal cell carcinoma; systemic therapies; risk stratification; efficacy;
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7 safety.
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10 11 **Strengths and limitations of this study** 12

- 13 ▶ This is the first network analysis to compare systemic treatments for
14 advanced/metastatic RCC separately by risk groups.
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- 16 ▶ Various statistical models were applied to synthesize data. The reliability and
17 accuracy of results were corroborated by the low statistical heterogeneity and
18 excellent model fit.
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- 20 ▶ Assessment of both efficacy and adverse events provides new insights into the
21 benefit-harm balance of different systemic treatments.
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- 23 ▶ Main limitation lies in the reporting quality of trials included.
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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

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

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14 In the present study, we performed a Bayesian network meta-analysis to compare
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16 first-line systemic treatments for advanced/metastatic RCC of favorable-,
17
18 intermediate-, and poor-risk, respectively. Network meta-analysis enables indirect
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20 comparisons based on a common comparator treatment when a head-to-head trial is
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22 unavailable and integrates direct and indirect comparisons to compare several
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24 treatment strategies while fully respecting randomization [21 22]. We aimed to
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26 summarize and compare the efficacy and safety associated with currently available
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28 systemic therapies for treating advanced/metastatic RCC of different risk categories
29
30 using network meta-analysis.

31 32 33 **2. Methods**

34 35 *2.1. Literature-search strategy*

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

48 49 50 *2.2. Inclusion and exclusion criteria*

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

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4 therapies alone or in combination. Relevant interventions included, but were not
5 restricted to: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab, ipilimumab,
6 axitinib, tivozanib, everolimus, temsirolimus, or bevacizumab plus IFN- α . Previous
7 systemic therapy for advanced/metastatic RCC was not allowed; (3) one or more of
8 the outcomes of interest mentioned below were reported. Nonoriginal articles,
9 duplicate reports and non-RCTs were excluded.
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17 *2.3. Data Extraction and Quality Assessment*

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19 Two researchers (GH. Cao and XQ. Wu) examined the manuscripts of included
20 trials independently, and extracted data into a structured form, including patient
21 characteristics, treatment strategies, and interest outcomes [progress free survival
22 (PFS), overall survival (OS), high-grade (grade ≥ 3) and overall drug-related adverse
23 events]. We gave priority to extracting data from intention-to-treat analyses. The
24 methodological quality of included RCTs was assessed using the Cochrane risk of
25 bias assessment tool [24]. Disagreement between investigators was resolved by
26 consensus.
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37 *2.4. Data synthesis and analysis*

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39 First, we performed traditional meta-analyses to compare the treatments using Stata
40 v.12 (StataCorp, College Station, TX, USA). We applied the chi-square test and the I^2
41 statistic to investigate the possibility of heterogeneity among studies. A P value < 0.10
42 or an $I^2 > 50\%$ suggested the presence of substantial heterogeneity.
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47 Second, we did Bayesian network meta-analyses. For meta-analysis of PFS and OS,
48 the reported adjusted hazard ratios (HRs) with 95% CIs were applied as the outcome
49 measure. For studies not reporting HRs, we calculated them from Kaplan-Meier curve
50 and information on follow-up with the pragmatic approach reported by Tierney et al
51 [25]. For drug-related adverse events, we calculated odds ratios (ORs) using the
52 available raw data abstracted from the trials. Both random-effects and fixed-effects
53 models were performed for the analyses [26]. Goodness of model fit was assessed
54 using the deviance information criterion and between-study standard deviation [26
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4 27]. Convergence was determined graphically according to the method described by
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6 Gelman *et al* [28].

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8 It is believed that certain systemic treatments are effective in certain risk groups
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10 than others, for example sunitinib is more effective in favorable-risk patients and
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12 nivolumab plus ipilimumab is more effective in intermediate and poor-risk patients
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14 [29], suggesting that there is a treatment-by-risk group (favorable-, intermediate-, and
15
16 poor-risk groups) interaction. Taking no account of this possible interaction in the
17
18 analysis, transitivity assumption across all included trials would be violated.
19
20 Therefore, we performed all network analyses separately by risk groups (favorable-,
21
22 intermediate-, and poor-risk groups) according to the MSKCC or IMDC risk model to
23
24 assure transitivity assumption.

25
26 One key assumption for network analysis is that direct and indirect comparisons do
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28 not disagree beyond chance [26 30]. To explore for evidence of inconsistency in the
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30 network, investigators compared the estimated treatment effects from the entire
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32 network with traditional pair-wise estimates [30]. Sensitivity analyses were performed
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34 restricted to trials that assessed approved systemic therapies (sunitinib, sorafenib,
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36 pazopanib, cabozantinib, axitinib, everolimus, temsirolimus, bevacizumab plus IFN- α ,
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38 and nivolumab plus ipilimumab). Publication bias and small-study effects were
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40 assessed using funnel plots [31].

41
42 We performed the Bayesian network analysis using OpenBUGS version 3.2.2 for
43
44 PFS, and Gemtc version 0.14.3 (van Valkenhoef *et al*, 2012) for adverse events. For
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46 PFS, we applied 15 000 iterations obtained after a training phase of 10 000-iteration.
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48 In order to minimize autocorrelation, we applied a thinning interval of 50 for each
49
50 chain. For adverse events, we applied the 60 000 iterations after a training phase of 40
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52 000 iterations. The treatments were ranked in terms of PFS, OS, and high-grade AEs,
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54 respectively, using the surface under the cumulative ranking curve (SUCRA) and the
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56 distribution of the ranking probabilities [32].
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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

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4 patients reported adequate information on progression-free survival and contributed to
5 network meta-analysis (Fig. 2A)[10-13 15 16 34-37 39-42]. Fig. 2B summarizes the
6 results of the network meta-analysis for PFS. Compared with sunitinib, IFN- α and
7 nivolumab plus ipilimumab were associated with significantly worse PFS (HR 2.69,
8 95% CI 1.54-4.67; and HR 2.18, 95% CI 1.47-3.25, respectively). Network
9 meta-analysis showed that only avelumab plus axitinib was associated with a
10 significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.34-0.96).
11 Based on the results of ranking, there was a 45% chance that avelumab plus axitinib
12 provided the greatest PFS benefit for patients with favorable-risk disease (SUCRA =
13 92.3%)(Fig. 2C).
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25 3.2.2. For advanced/metastatic RCC of intermediate-risk, 14 trials enrolling 5 473
26 total patients contributed to the analysis of PFS (Fig. 3A) [10-13 15 16 33-37 39 40
27 42]. Network meta-analysis demonstrated that cabozantinib, nivolumab plus
28 ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib were associated
29 with significantly higher improvement in PFS than sunitinib (HR 0.63, 95% CI
30 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
31 0.47-0.83, respectively). Everolimus, bevacizumab plus IFN- α , and temsirolimus plus
32 bevacizumab were significantly less efficacious for PFS than sunitinib (HR 1.50, 95%
33 CI 1.11-2.01; HR 1.69, 95% CI 1.18-2.41; HR 1.88, 95% CI 1.22-2.81, respectively)
34 (Fig. 3B). Based on the analysis of ranking, pembrolizumab plus axitinib had the
35 highest probability (49%) to be the best treatment for intermediate-risk patients
36 (SUCRA = 90.7%). Avelumab plus axitinib and cabozantinib had a similar likelihood
37 of being the second-best option for patients with intermediate-risk disease (Fig. 3C).
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51 3.2.3. Based on data that was available for advanced/metastatic RCC of poor-risk, the
52 network involved seven trials comparing nine different treatments (721 total patients;
53 Fig. 4A) [15 16 33-35 37 39 40 42]. Network meta-analysis demonstrated that
54 nivolumab plus ipilimumab and pembrolizumab plus axitinib were associated with
55 significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.43-0.76;
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4 HR 0.48, 95% CI 0.30-0.82, respectively) (Fig. 4B). On the base of ranking analysis,
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6 there was a 60% probability that pembrolizumab plus axitinib had the greatest PFS for
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8 poor-risk patients (SUCRA = 91.3%) (Fig. 4C).
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10 11 3.3. Overall survival

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13 Five RCTs reported OS according to risk subgroups, and data from three of them
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15 contributed to the network meta-analysis (572, 1801, and 407 patients for favorable-,
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17 intermediate-, and poor-risk, respectively)[16 38 39]. For advanced/metastatic RCC of
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19 favorable-risk, there is no significant OS benefit between sunitinib and pazopanib
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21 (HR 0.88, 95% CI 0.64-1.21) or pembrolizumab plus axitinib (HR 0.64, 95% CI
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23 0.24-1.70) (Fig. 5A). For intermediate-risk patients, pembrolizumab plus axitinib and
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25 nivolumab plus ipilimumab were associated with significantly higher improvement in
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27 OS than sunitinib (HR 0.53, 95% CI 0.34-0.81; HR 0.66, 95% CI 0.50-0.87,
28
29 respectively)(Fig. 5B). For advanced/metastatic RCC of poor-risk, pembrolizumab
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31 plus axitinib and nivolumab plus ipilimumab were significantly more efficacious for
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33 OS than sunitinib (HR 0.43, 95% CI 0.23-0.80; HR 0.57, 95% CI 0.39-0.83,
34
35 respectively) (Fig. 5C). Based on the results of ranking, there were 81% and 78%
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37 probabilities for pembrolizumab plus axitinib to be the best choice for intermediate-
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39 and poor-risk patients, respectively (SUCRA =93.1% ; SUCRA= 91.4%, respectively)
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41 (appendix Fig.1-3).
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45 3.4. Adverse events

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47 Nine trials contributed to our analysis of overall and high-grade drug-related adverse
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49 events [10 11 13 15 16 36 39-41]. All the nine trials did not provide adverse events
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51 data for different risk groups, so we extracted a summary of adverse event data.
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53 Results of comparisons of adverse events of nine systemic treatments are presented in
54
55 Fig. 6 and appendix Fig. 4 Stepwise comparison of all the seven therapies did not find
56
57 significant differences in rates of high-grade or overall adverse events. The most
58
59 common adverse events included diarrhea, hypertension, fatigue, and decreased
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61 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

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4 been approved for treating advanced RCC: sunitinib, sorafenib, pazopanib,
5 cabozantinib, axitinib, everolimus, temsirolimus, and bevacizumab (in combination
6 with IFN- α).
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9 As shown in this analysis, for patients with intermediate-risk, sunitinib resulted in a
10 significant PFS benefit compared with everolimus. The varied clinical benefit could
11 be associated with mechanisms of action of TKI and mTOR inhibitor. Sunitinib not
12 only inhibit VEGF receptors -1, -2, and -3, which may be the most clearly relevant
13 targets in RCC so far, but also exhibit potent activity against PDGF receptor [11 45]. It
14 has been reported that PDGF plays a critical role in the recruitment of pericytes to
15 sprouting tumor vessels, and pericyte-covered vessels are more likely resistant to
16 anti-vascular therapy than those pericyte-negative vessels [46 47]. The mTOR
17 complex is the upstream of an intracellular signaling network regulating cell growth
18 and angiogenesis, and it plays a key role in the pathogenesis of advanced/metastatic
19 RCC [48]. It has been demonstrated that rapamycin analogs, including everolimus and
20 temsirolimus, inhibit only one of two signaling complexes of mTOR [49]. The
21 mTORC1 signaling is potently inhibited by everolimus and temsirolimus, while the
22 mTORC2 signaling is not [50]. Consequently, one downstream signaling of mTOR
23 activation is unopposed. The relatively unsatisfactory efficacy should disable the
24 mTOR inhibitors as more suitable therapies for the treatment of advanced/metastatic
25 RCC than TKIs. Regarding TKIs, our results suggest that sunitinib was most likely to
26 be the best treatment regimen for patients with favorable-risk disease.
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30 A potentially additive benefit from combinations of targeted drugs has been
31 suggested on the basis that they inhibit separate cellular pathways. However, our
32 results show that temsirolimus plus bevacizumab, and bevacizumab plus IFN- α
33 provide little survival benefit compared with sunitinib, further confirming absence of
34 evidence that combination treatment simultaneously inhibiting both VEGF and
35 mTOR signaling results in therapeutic synergy [18 20 37].
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39 Immune checkpoint antibodies block the inhibitory T-cell receptor programmed
40 death-1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4)-signaling to augment
41 tumor specific immune response [51]. Nivolumab (an anti-PD-1 antibody) is
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4 approved for the treatment of advanced RCC in the second line setting. Ipilimumab
5 (an anti-CTLA-4 antibody) is approved for the treatment of advanced melanoma.
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7 Nivolumab plus ipilimumab has been reported significant efficacy in multiple tumor
8
9 types [52-53]. In this analysis, pembrolizumab plus axitinib appeared to be the
10
11 optimum treatment for intermediate- and poor-risk patients. Single-agent anti-tumor
12
13 activity of pembrolizumab and axitinib for mRCC has been reported in previous
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15 studies [12-54]. Accordingly, axitinib in combination with pembrolizumab was
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17 assessed and contributed to objective response rate in 73% patients in a phase 1b trial
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19 [55]. Our result was consistent with results of KEYNOTE-426 trial, demonstrating
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21 that pembrolizumab plus axitinib resulted in significant OS and PFS benefit compared
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23 with sunitinib [39]. In addition, the survival benefit of pembrolizumab plus axitinib
24
25 was observed independent of PD-L1 status [39].
26

27 Pembrolizumab plus axitinib is a combination of anti-PD-1 monoclonal antibody
28
29 and VEGF receptor TKI. Immune checkpoint inhibitors (ICI) block the inhibitory
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31 T-cell receptor PD-1 or CTLA-4-signaling to augment tumor specific immune
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33 response [51]. Besides of antiangiogenic effects, VEGF inhibition could enhance the
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35 recruitment and infiltration of immune cells into the tumors [56-57]. It's reported that
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37 simultaneous blockade of PD-1 and VEGF receptor-2 induced decreased tumor
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39 neovascularization and tumor inhibition in a murine model [58]. These studies
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41 suggested that the combination of ICI and VEGF receptor inhibitors could provide
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43 enhanced benefit for mRCC. Recently, in addition to pembrolizumab plus axitinib,
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45 avelumab (anti-PD-L1 antibody) plus axitinib, and atezolizumab (anti-PD-L1
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47 antibody) plus bevacizumab were respectively assessed in two phase 3 RCTs
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49 (IMmotion 151 and JAVELIN Renal 101), and both of them showed significant
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51 survival benefit for mRCC compared with sunitinib [39-59]. However, there is no
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53 head-to-head trial comparing combinations of ICI and VEGF receptor inhibitors
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55 inhibitors (pembrolizumab plus axitinib, avelumab plus axitinib, and atezolizumab plus
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57 bevacizumab) directly. In consistent with our previous study, the present analysis
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59 revealed that pembrolizumab plus axitinib presented the highest OS benefit for
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intermediate- and poor-risk patients. For advanced/metastatic RCC of favorable-risk,

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4 only avelumab plus axitinib was associated with a significantly higher improvement
5 in PFS than sunitinib, suggesting avelumab plus axitinib might be the optimum
6 treatment for favorable-risk patients. Considering patients continued to be followed
7 for OS in the JAVELIN Renal 101 trial [40], the real OS benefit for avelumab plus
8 axitinib over sunitinib requires additional follow-up.
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13 Recently, several network meta-analyses were attempted to investigate the
14 comparative effects of different systemic agents for treatment of advanced/metastatic
15 RCC [60-63]. However, trials included in the meta-analyses enrolled patients with
16 different risk groups. The analysis used aggregate data and did not perform subgroup
17 analysis based on risk strata. In the present study, we performed a network
18 meta-analysis to compare first-line systemic treatments for advanced/metastatic RCC
19 of favorable-, intermediate-, and poor-risk, respectively, thus providing physicians
20 with the optimal treatment for different risk groups.
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29 The strengths of our study are as follows. To the best of our knowledge, this study
30 is the first network analysis to compare systemic treatments for advanced/metastatic
31 RCC separately by risk groups. We applied multiple rigorous search strategies to
32 retrieve all potentially eligible RCTs. In the present study, we comprehensively
33 compared and ranked all available first-line systemic therapies for
34 advanced/metastatic RCC of favorable-, intermediate-, and poor-risk, respectively,
35 thus providing physicians with an overall appraisal of systemic therapies for different
36 risk groups. In addition, we used Bayesian network meta-analysis to synthesize data.
37 This approach provides indirect effect estimates in the absence of head-to-head trial
38 and incorporates all available information from RCTs while fully maintaining
39 randomization [21 22]. We applied various statistical models to increase reliability of
40 the results. Results were consistent across all analyzed outcomes. Moreover, the
41 reliability and accuracy of results were corroborated by the low statistical
42 heterogeneity and excellent model fit. Finally, assessment of both efficacy and
43 adverse events provides new insights into the benefit-harm balance of different
44 systemic treatments.
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However, the limitations of our study must be taken into account. The major

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4 limitation of this network meta-analysis lies in the reporting quality of trials reviewed.
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6 Ten included trials were not masked, which might affect the validity of our findings.
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8 In addition, three included trials (CABOSUN, ROSORC, and RECORD-3) are phase
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10 2 RCTs with smaller sample size, and they may be less authoritative compared with
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12 phase 3 RCTs. Moreover, most of the trials did not perform the analysis of OS in risk
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14 subgroup, which made it impossible to assess the OS benefits of all the existing
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16 treatments for different risk patients. In addition, this meta-analysis was conducted
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18 based on summary statistics rather than individual patient level data. There might be
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20 some confounding factors (*e.g.*, ethnic origin, prior nephrectomy, *etc.*) at the
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22 individual patient level that might influence the benefit of systemic treatments, but
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24 were not available; therefore analyses adjusted for these factors were impossible in
25
26 our network meta-analysis. Access to patient-level longitudinal data would allow us to
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28 establish more robust and accurate conclusions in specific subgroups of patients.
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30 Moreover, the length of follow-up varied across studies, resulting in potential
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32 variations in survival benefits and adverse events. Due to only eight trials reporting
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34 median follow-up, sensitivity analyses adjusted for this factor were impossible.
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36 Moreover, individual dosage varied across studies and data were too sparse to
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38 investigate effects of different schedules, which might somewhat affect the
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40 generalisability of our findings. Since the analysis was based on highly selected RCTs
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42 and the results were based on fixed-effects models, findings in this analysis may not
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44 be entirely generalized to real-world practice. Finally, findings in this meta-analysis
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46 were mainly based on patients with clear-cell advanced RCC, thus no robust
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48 recommendations can be provided for non-clear-cell subtypes. Two trials included
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50 small subsets of non-clear-cell histotypes (11% and 14% of the study population),
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52 which might somewhat damage the results of our analysis.
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54 **5. Conclusions**

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

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4 patients. Further well-designed, large-scale RCTs are required to confirm and update
5 the findings of this analysis.
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10 11 **Author Contributions**

12 G-HC and X-QW conceived and designed the meta-analysis, Z-ZW and X-YT
13 identified and acquired reports of trials, and extracted data. XW and H-TZ analyzed
14 and interpreted the data. CZ and G-PJ contacted authors of trials for additional
15 information. G-HC and X-QW drafted the manuscript. T-ZY critically reviewed the
16 manuscript. All authors approved the final submitted version of the report.
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27 in study design, data collection, data analysis, data interpretation, or writing of the
28 report.
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35 **Conflicts of Interest:** None declared.
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37

38 39 **Data Availability Statement**

40 All data relevant to the study are included in the article or uploaded as supplementary
41 information.
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46 47 **Patient and Public Involvement**

48 Patients or the public WERE NOT involved in the design, or conduct, or reporting, or
49 dissemination of our research.
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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)								
Eregorlimus	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)
Pirotto 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
Hasson 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)
Ngrier 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)

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3	Motzer 2018 (CheckMate 214)								
4	Nivolumab plus Ipilimumab	550	62 (26-85)	75	23	61	17	11.6 (8.7–15.5)	0.82(0.64-1.05) [†]
5	Sunitinib	546	62 (21-85)	72	23	61	16	8.4 (7.0–10.8)	1 (Ref)
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7	Choueiri 2017								
8	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)
9	Sunitinib	78	64(31-87)	73.1	0	80.8 [§]	19.2 [§]	5.6 (3.4 to 8.1)	1 (Ref)
10									
11	Motzer 2019 (JAVELIN Renal 101)								
12	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)
13	Sunitinib	444	61 (27-88)	77.5	22.5	66.0	10.1	8.4 (6.9-11.1)	1 (Ref)
14									
15	Rizvi 2019 (KEYNOTE-426)								
16	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)
17	Sunitinib	429	61 (26-90)	74.6	30.5 [§]	57.3 [§]	12.1 [§]	11.1 (8.7-12.5)	1 (Ref)

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

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

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31 **Legends for Figures**

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34 **Fig. 1 - Literature search and selection**

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

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

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4 = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI=
5 avelumab plus axitinib. Stepwise comparison of treatments did not find significant
6 differences in rates of high-grade adverse events.
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11 **Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis**
12 **for hazard ratios of progression-free survival**

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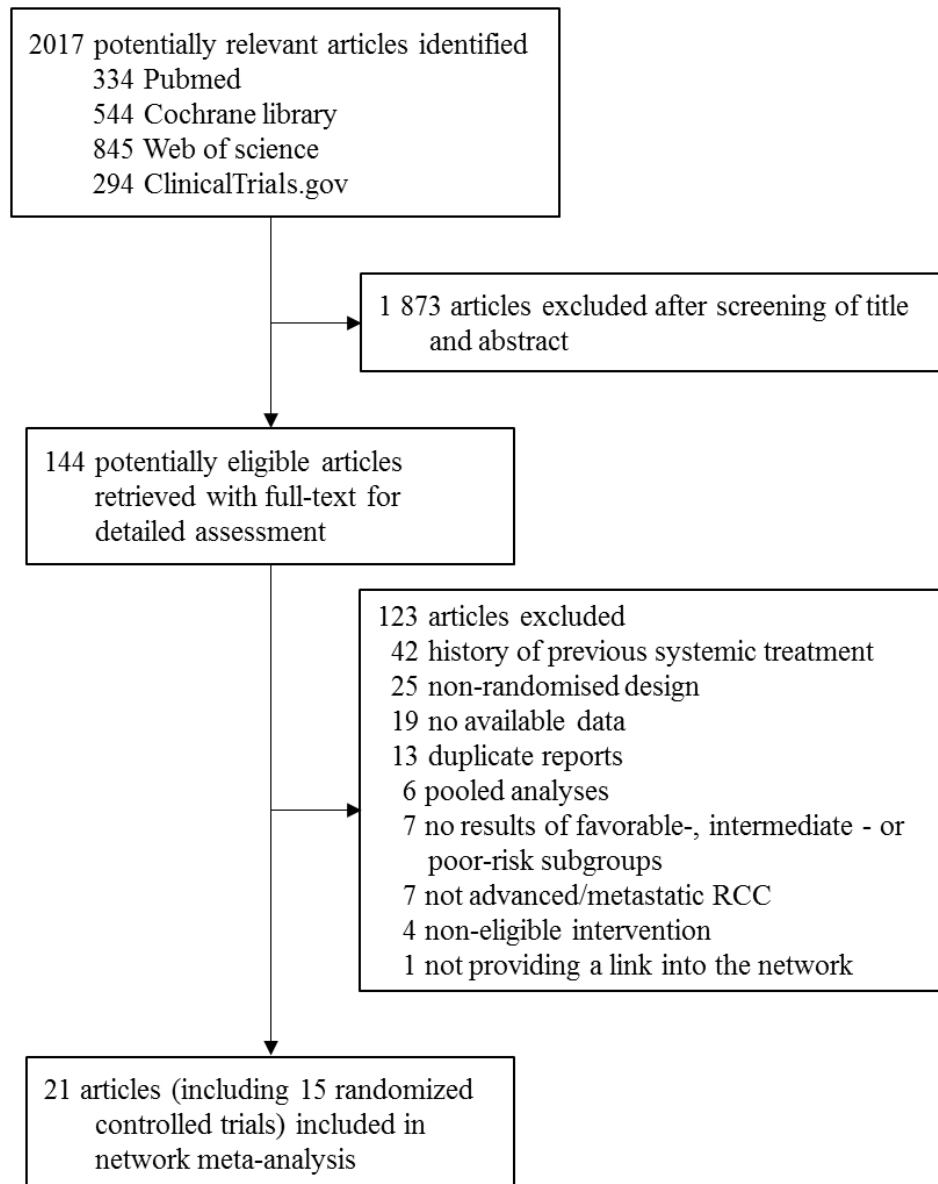


Fig. 1 - Literature search and selection

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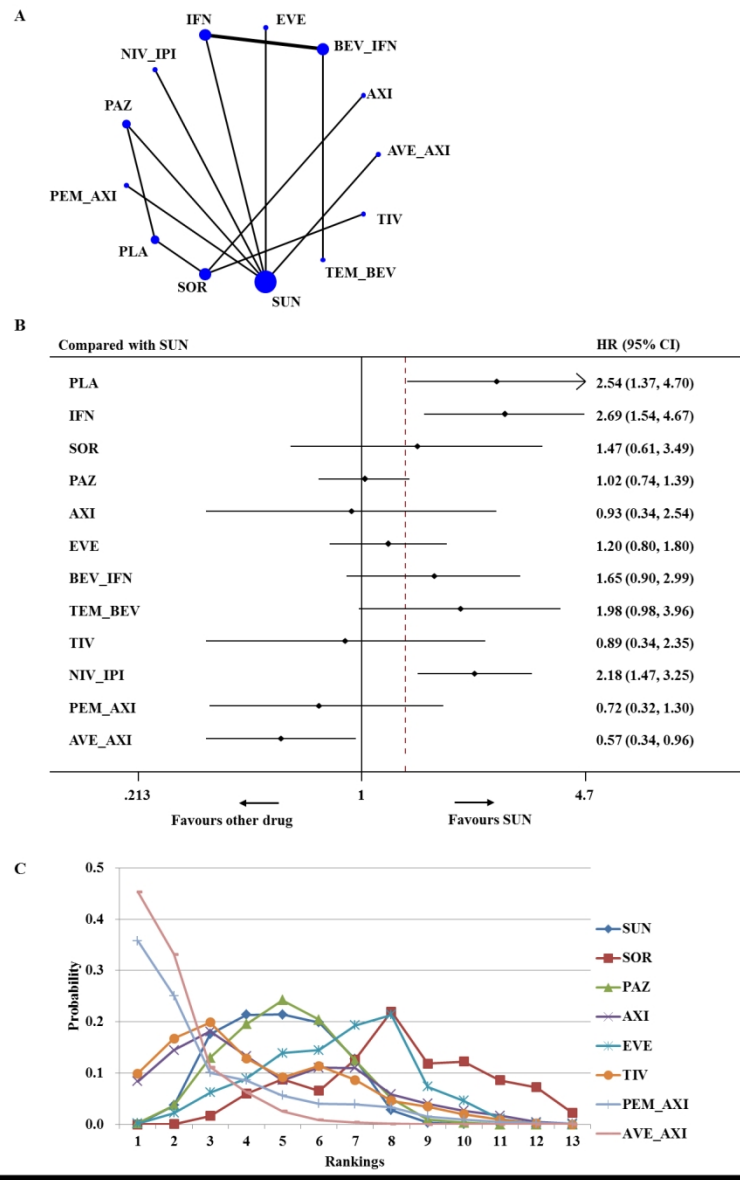


Fig. 2 - Analysis of progression-free survival for patients with favorable-risk disease. (A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) forest plot, with sunitinib as the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

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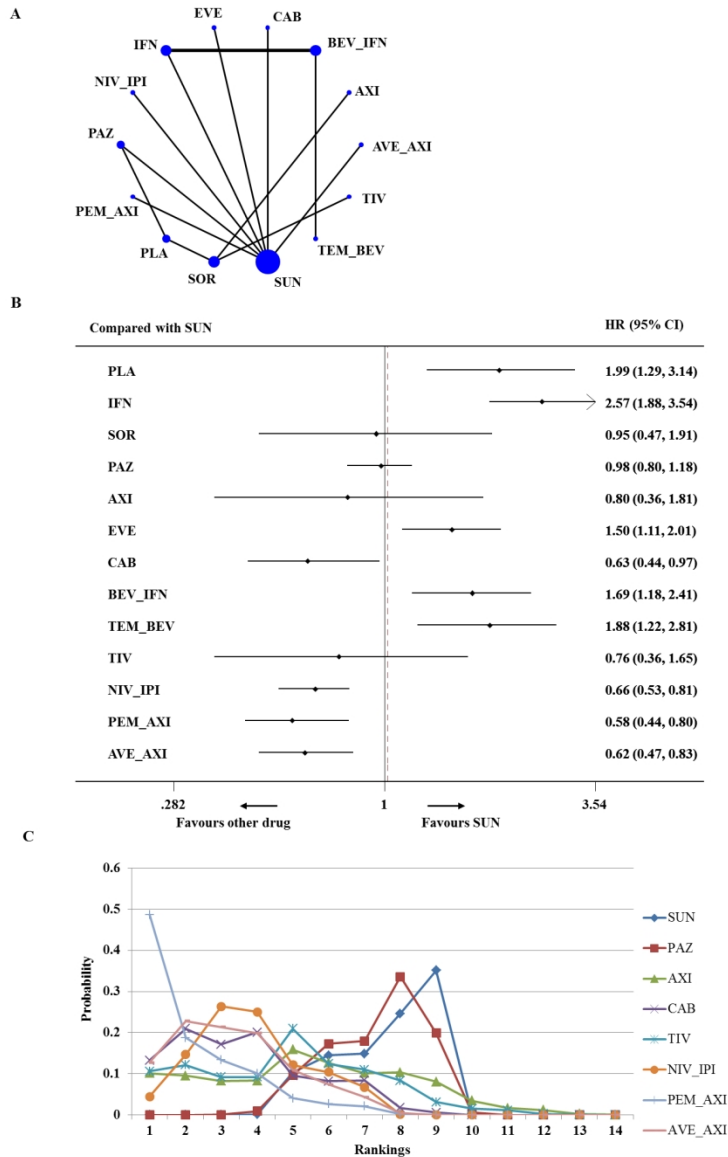


Fig. 3 - Analysis of progression-free survival for patients with intermediate-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. 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.

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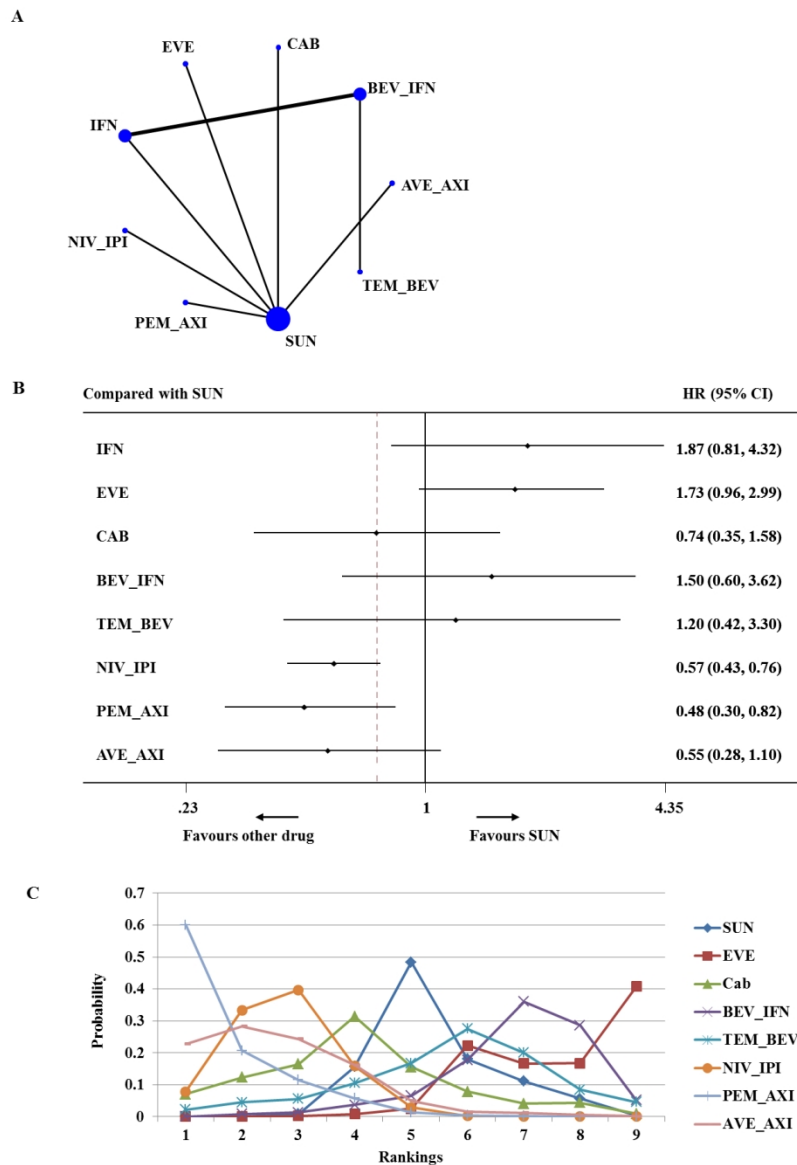


Fig. 4 - Analysis of progression-free survival for patients with poor-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. 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.

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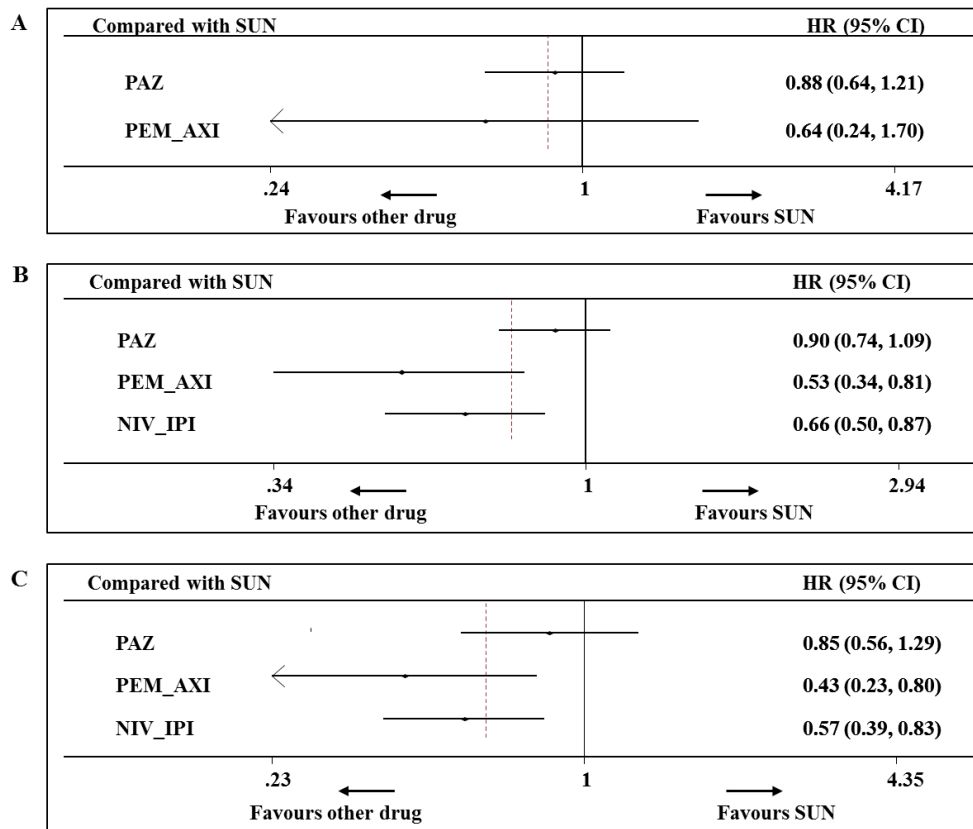


Fig.5- Analysis of overall survival for patients with favorable- risk (A), intermediate- risk (B), and poor-risk (C). HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab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

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SUN	0.40 (0.02, 8.55)	2.83 (0.06, 150.75)	1.07 (0.12, 9.19)	1.98 (0.02, 201.54)	0.92 (0.09, 8.13)	5.29 (0.06, 499.51)	0.49 (0.05, 4.26)	1.30 (0.15, 12.14)	1.00 (0.11, 8.77)
PLA		7.16 (0.63, 94.46)	2.67 (0.31, 24.54)	4.95 (0.20, 156.27)	2.30 (0.05, 99.17)	12.98 (0.45, 392.76)	1.24 (0.03, 52.88)	3.33 (0.08, 135.00)	2.48 (0.06, 109.18)
SOR			0.38 (0.01, 9.58)	0.69 (0.08, 6.50)	0.32 (0.00, 30.01)	1.82 (0.18, 16.55)	0.17 (0.00, 13.75)	0.46 (0.00, 39.97)	0.36 (0.00, 30.63)
PAZ				1.84 (0.04, 110.86)	0.87 (0.03, 19.18)	4.87 (0.09, 278.21)	0.46 (0.02, 10.04)	1.22 (0.06, 25.58)	0.92 (0.04, 19.41)
TIV					0.46 (0.00, 67.33)	2.63 (0.11, 53.00)	0.25 (0.00, 33.35)	0.66 (0.00, 91.27)	0.51 (0.00, 67.33)
CAB						5.80 (0.03, 947.65)	0.53 (0.02, 13.17)	1.42 (0.06, 33.89)	1.08 (0.05, 25.63)
SOR_IL-2							0.09 (0.00, 13.57)	0.25 (0.00, 40.53)	0.19 (0.00, 28.00)
NIV_IPI								2.65 (0.13, 58.75)	2.04 (0.09, 44.95)
PEM_AXI									0.76 (0.03, 16.68)
AVE_AXI									

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)

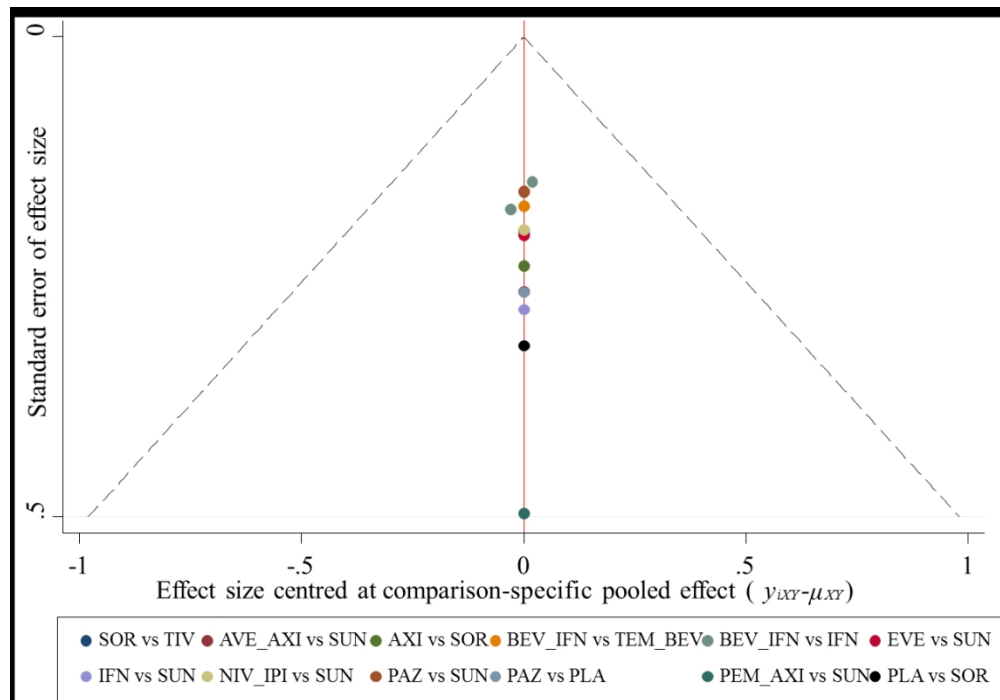


Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis for hazard ratios of progression-free survival
 SUN = sunitinib. PLA = placebo. IFN = interferon- α . SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon- 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 cabozantinib: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: (cabozantinib)) 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

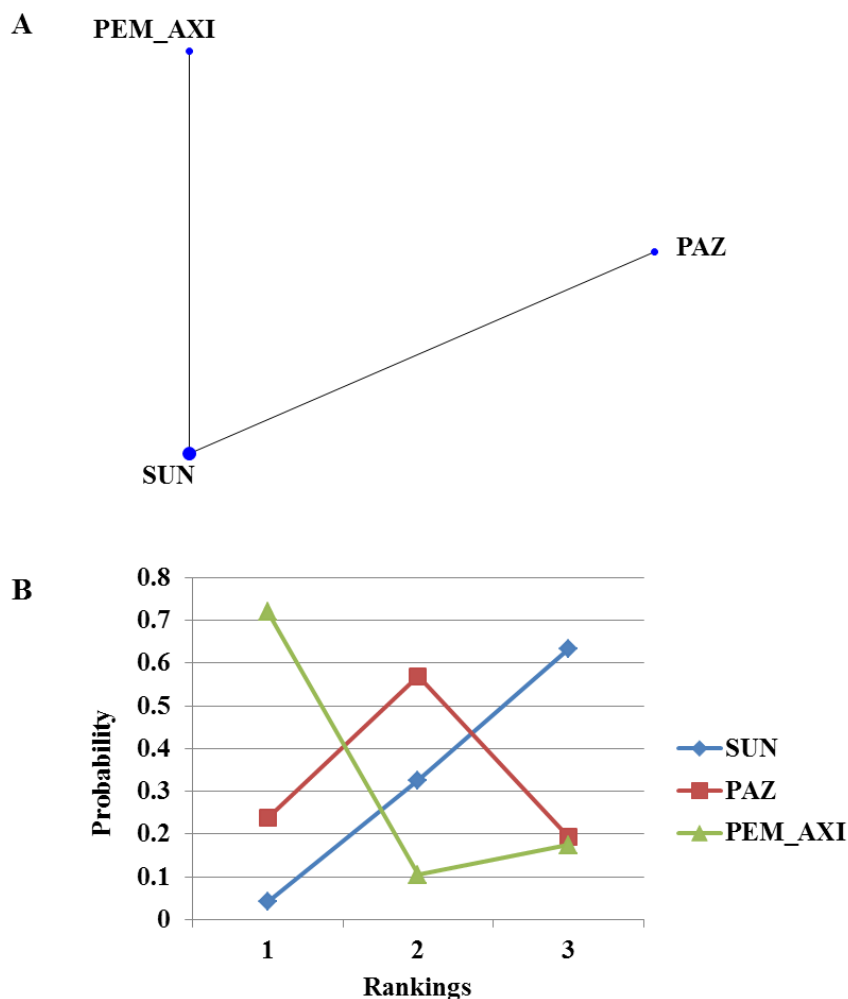
ClinicalTrials.gov:

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

(<http://clinicaltrials.gov/>)

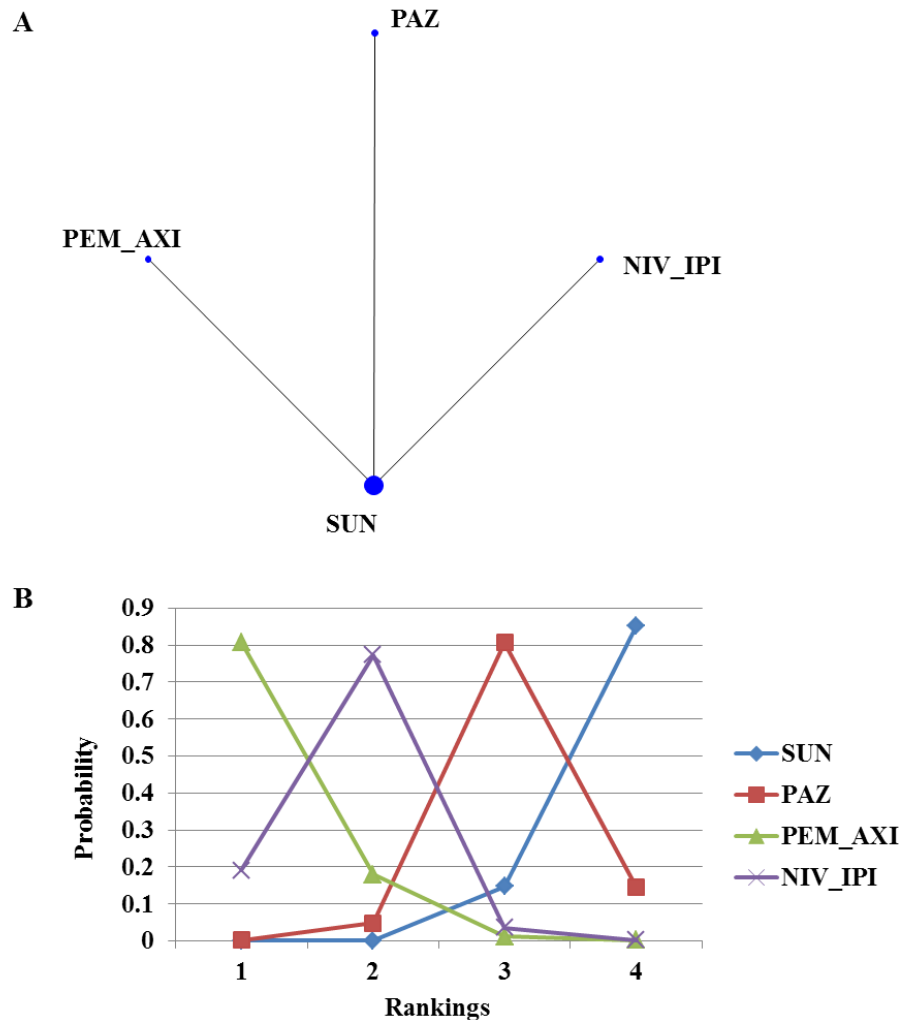
For peer review only

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



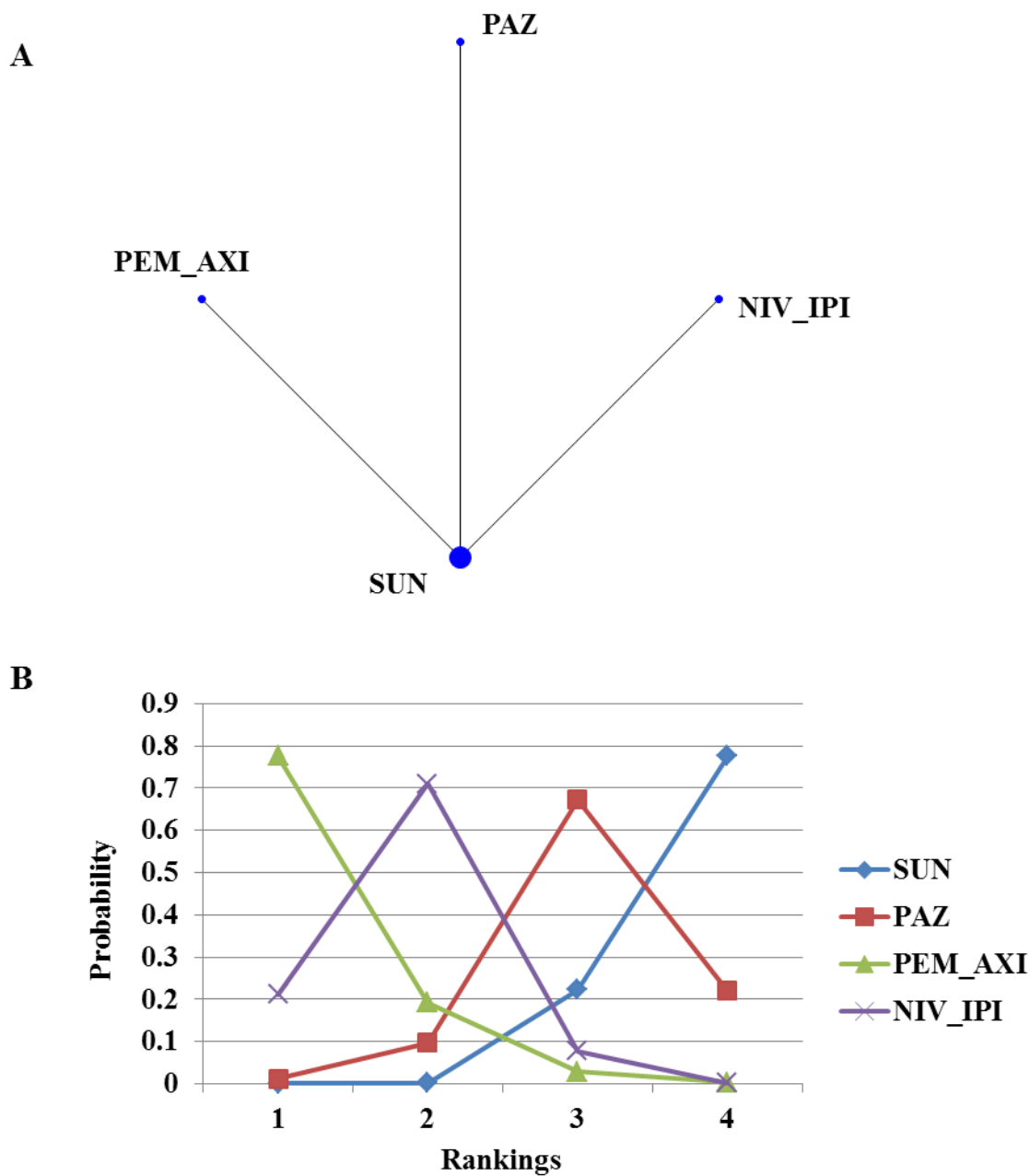
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. 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.



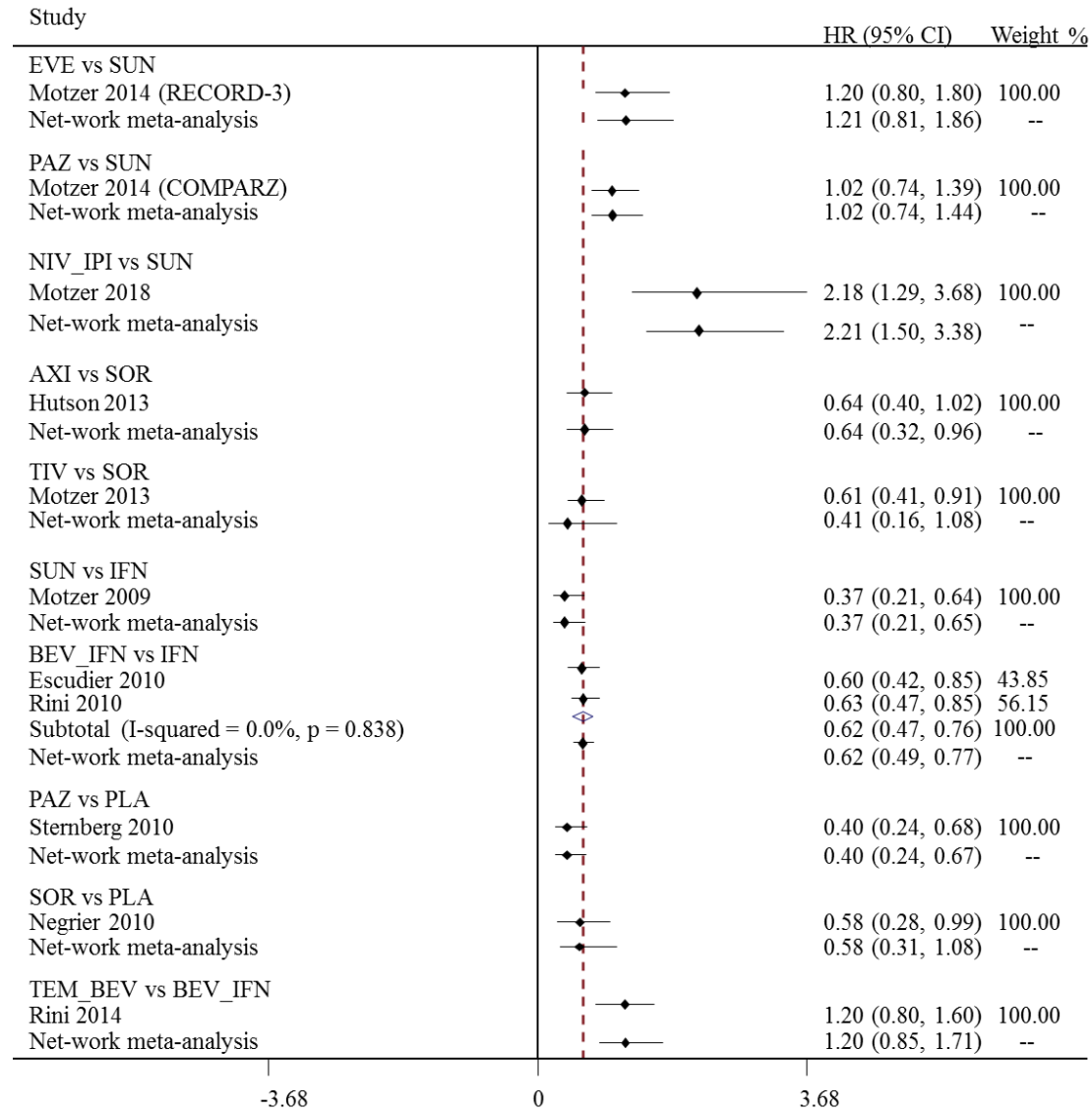
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. 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

SUN	2.28 (0.27, 23.95)	1.05 (0.03, 45.23)	0.34 (0.08, 1.40)	0.38 (0.05, 2.41)	1.61 (0.17, 19.17)
	PAZ	0.46 (0.01, 34.72)	0.15 (0.01, 1.94)	0.16 (0.01, 2.69)	0.68 (0.03, 18.38)
		CAB	0.33 (0.01, 14.72)	0.36 (0.00, 18.55)	1.57 (0.02, 115.31)
			NIV_IPI	1.12 (0.10, 11.68)	4.77 (0.32, 84.86)
				PEM_AXI	4.31 (0.22, 98.04)
					AVE_AXI

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Choueiri 2017	+	+	-	+	+	+	?
Escudier 2010 (AVOREN)	+	+	+	+	+	+	?
Hutson 2013	+	+	-	+	+	+	+
Motzer 2009	+	+	-	?	+	+	+
Motzer 2013	+	+	-	?	+	+	?
Motzer 2014 (COMPARZ)	+	+	-	?	+	+	+
Motzer 2014 (RECORD-3)	+	?	-	?	+	+	?
Motzer 2018 (CheckMate 214)	+	+	?	+	+	+	?
Motzer 2019 (JAVELIN Renal 101)	+	+	-	+	+	+	+
Negrier 2010 (TARGET)	+	+	+	+	+	+	+
Procopio 2013 (ROSORC)	+	+	-	-	+	+	?
Rini 2010 (CALGB 90206)	+	+	+	+	+	+	+
Rini 2014 (INTORACT)	+	+	-	+	+	+	+
Rini 2019 (KEYNOTE-426)	+	+	-	+	+	+	+
Sternberg 2010 (VEG105192)	+	+	+	+	+	+	?

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

Page 1 of 2

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

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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

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Primary Subject Heading:	Urology
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Keywords:	Urological tumours < UROLOGY, Kidney tumours < ONCOLOGY, IMMUNOLOGY

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

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5 **Keywords:** renal cell carcinoma; systemic therapies; risk stratification; efficacy;
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7 safety.
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10 11 **Strengths and limitations of this study** 12

- 13 ▶ This is the first network analysis to compare systemic treatments for
14 advanced/metastatic RCC separately by risk groups.
15
- 16 ▶ Various statistical models were applied to synthesize data. The reliability and
17 accuracy of results were corroborated by the low statistical heterogeneity and
18 excellent model fit.
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- 20 ▶ Assessment of both efficacy and adverse events provides new insights into the
21 benefit-harm balance of different systemic treatments.
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- 23 ▶ Main limitation lies in the reporting quality of trials included.
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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

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

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14 In the present study, we performed a Bayesian network meta-analysis to compare
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16 first-line systemic treatments for advanced/metastatic RCC of favorable-,
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18 intermediate-, and poor-risk, respectively. Network meta-analysis enables indirect
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20 comparisons based on a common comparator treatment when a head-to-head trial is
21
22 unavailable and integrates direct and indirect comparisons to compare several
23
24 treatment strategies while fully respecting randomization [21 22]. We aimed to
25
26 summarize and compare the efficacy and safety associated with currently available
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28 systemic therapies for treating advanced/metastatic RCC of different risk categories
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30 using network meta-analysis.

31 32 33 **2. Methods**

34 35 *2.1. Literature-search strategy*

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

48 49 50 *2.2. Inclusion and exclusion criteria*

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

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4 therapies alone or in combination. Relevant interventions included, but were not
5 restricted to: sorafenib, sunitinib, pazopanib, cabozantinib, nivolumab, ipilimumab,
6 axitinib, tivozanib, everolimus, temsirolimus, or bevacizumab plus IFN- α . Previous
7 systemic therapy for advanced/metastatic RCC was not allowed; (3) one or more of
8 the outcomes of interest mentioned below were reported. Nonoriginal articles,
9 duplicate reports and non-RCTs were excluded.
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17 *2.3. Data Extraction and Quality Assessment*

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19 Two researchers (GH. Cao and XQ. Wu) examined the manuscripts of included
20 trials independently, and extracted data into a structured form, including patient
21 characteristics, treatment strategies, and interest outcomes [progress free survival
22 (PFS), overall survival (OS), high-grade (grade ≥ 3) and overall drug-related adverse
23 events]. The patient characteristics, treatment strategies, PFS and OS were extracted
24 at the study-level for meta-analyses even if the patient-level were available. For
25 drug-related adverse events, the patient-level data were extracted for meta-analyses.
26 We gave priority to extracting data from intention-to-treat analyses. The
27 methodological quality of included RCTs was assessed using the Cochrane risk of
28 bias assessment tool [24]. Disagreement between investigators was resolved by
29 consensus.
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43 *2.4. Data synthesis and analysis*

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45 First, we performed traditional meta-analyses to compare the treatments using Stata
46 v.12 (StataCorp, College Station, TX, USA). We applied the chi-square test and the I^2
47 statistic to investigate the possibility of heterogeneity among studies. A P value < 0.10
48 or an $I^2 > 50\%$ suggested the presence of substantial heterogeneity.
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53 Second, we did Bayesian network meta-analyses. For meta-analysis of PFS and OS,
54 the reported adjusted hazard ratios (HRs) with 95% CIs were applied as the outcome
55 measure. For studies not reporting HRs, we calculated them from Kaplan-Meier curve
56 and information on follow-up with the pragmatic approach reported by Tierney et al
57 [25]. For drug-related adverse events, we calculated odds ratios (ORs) using the
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4 available patient-level data abstracted from the trials. Both random-effects and
5 fixed-effects models were performed for all Bayesian network meta-analyses [26].
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7 Goodness of model fit was assessed using the deviance information criterion and
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9 between-study standard deviation [26 27]. Convergence was determined graphically
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11 according to the method described by Gelman *et al* [28].
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14 It is believed that certain systemic treatments are effective in certain risk groups
15 than others, for example sunitinib is more effective in favorable-risk patients and
16 nivolumab plus ipilimumab is more effective in intermediate and poor-risk patients
17 [29], suggesting that there is a treatment-by-risk group (favorable-, intermediate-, and
18 poor-risk groups) interaction. Taking no account of this possible interaction in the
19 analysis, transitivity assumption across all included trials would be violated.
20
21 Therefore, we performed all network analyses separately by risk groups (favorable-,
22 intermediate-, and poor-risk groups) according to the MSKCC or IMDC risk model to
23 assure transitivity assumption.
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31 One key assumption for network analysis is that direct and indirect comparisons do
32 not disagree beyond chance [26 30]. To explore for evidence of inconsistency in the
33 network, investigators compared the estimated treatment effects from the entire
34 network with traditional pair-wise estimates [30]. Sensitivity analyses were performed
35 restricted to trials that assessed approved systemic therapies (sunitinib, sorafenib,
36 pazopanib, cabozantinib, axitinib, everolimus, temsirolimus, bevacizumab plus IFN- α ,
37 and nivolumab plus ipilimumab). Publication bias and small-study effects were
38 assessed using funnel plots [31].
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47 We performed the Bayesian network analysis using OpenBUGS version 3.2.2 for
48 PFS, and Gemtc version 0.14.3 (van Valkenhoef *et al*, 2012) for adverse events. We
49 performed fewer iterations for PFS to reduce computational burden without loss of
50 convergence and model fit. For PFS, we applied 15 000 iterations obtained after a
51 training phase of 10 000-iteration. In order to minimize autocorrelation, we applied a
52 thinning interval of 50 for each chain. For adverse events, we applied the 60 000
53 iterations after a training phase of 40 000 iterations. The treatments were ranked in
54 terms of PFS, OS, and high-grade AEs, respectively, using the surface under the
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4 cumulative ranking curve (SUCRA) and the distribution of the ranking probabilities
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10 11 **3. Results** 12

13 14 *3.1. Search results and study characteristics* 15

16 The literature search yielded 2 017 potentially eligible studies, of which 1 873 were
17 excluded based on screening titles and abstracts (Fig. 1). The full text of 144
18 remaining studies were analyzed, and finally 21 publications reporting 15 unique
19 RCTs were included (Table), involving 8 995 participants randomly assigned to one
20 of the 13 treatment strategies: sorafenib, sunitinib, pazopanib, cabozantinib,
21 nivolumab plus ipilimumab, axitinib, tivozanib, everolimus, IFN- α , bevacizumab plus
22 IFN- α , temsirolimus plus bevacizumab, avelumab plus axitinib, and pembrolizumab
23 and axitinib. According to the MSKCC or IMDC criteria, there were 2 783, 5 474 and
24 721 participants had favorable-, intermediate-, and poor-risk disease, respectively.
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33 The main characteristics of included RCTs are summarized in Table. The
34 demographic characteristics of patients were well balanced across trials. Enrolled
35 patients across trials were similar in terms of age, gender, and risk classification.
36 Across trials, the median age of patients ranged from 58 to 64 years. The participants
37 were predominantly male (71.7%, 6 451 of 8 995). The included trials were designed
38 similarly. Median follow-up ranged from 10.7 to 58 months. The mean sample sizes
39 were 100, 192 and 32 patients per group for favorable-, intermediate- and poor-risk
40 subtypes, respectively. Thirteen trials selected for clear-cell carcinoma subtypes
41 [10-12 15 16 33-40], and two trials also included small subsets of non-clear-cell
42 histotypes, each comprising 11% and 14% of the study population, respectively [41
43 42]. All studies were two-arm trials. The dosages used in most of trials were within
44 the recommended dose ranges.
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56 In this network meta-analysis, results are reported based on fixed-effects models
57 because they demonstrated better goodness of fit compared with random-effects
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4 models. The results of random-effects models are available in appendix Table 1-5.
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7 8 *3.2. Progression-free survival*

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10 *3.2.1.* For advanced/metastatic RCC of favorable-risk, 13 trials enrolling 2 514 total
11 patients reported adequate information on progression-free survival and contributed to
12 network meta-analysis (Fig. 2A)[10-13 15 16 34-37 39-42]. Fig. 2B summarizes the
13 results of the network meta-analysis for PFS. Compared with sunitinib, IFN- α and
14 nivolumab plus ipilimumab were associated with significantly worse PFS (HR 2.69,
15 95% CI 1.54-4.67; and HR 2.18, 95% CI 1.47-3.25, respectively). Network
16 meta-analysis showed that only avelumab plus axitinib was associated with a
17 significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.34-0.96).
18 Based on the results of ranking, there was a 45% chance that avelumab plus axitinib
19 provided the greatest PFS benefit for patients with favorable-risk disease (SUCRA =
20 92.3%)(Fig. 2C).
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33 *3.2.2.* For advanced/metastatic RCC of intermediate-risk, 14 trials enrolling 5 473
34 total patients contributed to the analysis of PFS (Fig. 3A) [10-13 15 16 33-37 39 40
35 42]. Network meta-analysis demonstrated that cabozantinib, nivolumab plus
36 ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib were associated
37 with significantly higher improvement in PFS than sunitinib (HR 0.63, 95% CI
38 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
39 0.47-0.83, respectively). Everolimus, bevacizumab plus IFN- α , and temsirolimus plus
40 bevacizumab were significantly less efficacious for PFS than sunitinib (HR 1.50, 95%
41 CI 1.11-2.01; HR 1.69, 95% CI 1.18-2.41; HR 1.88, 95% CI 1.22-2.81, respectively)
42 (Fig. 3B). Based on the analysis of ranking, pembrolizumab plus axitinib had the
43 highest probability (49%) to be the best treatment for intermediate-risk patients
44 (SUCRA = 90.7%). Avelumab plus axitinib and cabozantinib had a similar likelihood
45 of being the second-best option for patients with intermediate-risk disease (Fig. 3C).
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3.2.3. Based on data that was available for advanced/metastatic RCC of poor-risk, the

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4 network involved seven trials comparing nine different treatments (721 total patients;
5 Fig. 4A) [15 16 33-35 37 39 40 42]. Network meta-analysis demonstrated that
6 nivolumab plus ipilimumab and pembrolizumab plus axitinib were associated with
7 significantly higher improvement in PFS than sunitinib (HR 0.57, 95% CI 0.43-0.76;
8 HR 0.48, 95% CI 0.30-0.82, respectively) (Fig. 4B). On the base of ranking analysis,
9 there was a 60% probability that pembrolizumab plus axitinib had the greatest PFS for
10 poor-risk patients (SUCRA = 91.3%) (Fig. 4C).
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19 3.3. Overall survival

20 Five RCTs reported OS according to risk subgroups, and data from three of them
21 contributed to the network meta-analysis (572, 1801, and 407 patients for favorable-,
22 intermediate-, and poor-risk, respectively)[16 38 39]. For advanced/metastatic RCC of
23 favorable-risk, there is no significant OS benefit between sunitinib and pazopanib
24 (HR 0.88, 95% CI 0.64-1.21) or pembrolizumab plus axitinib (HR 0.64, 95% CI
25 0.24-1.70) (Fig. 5A). For intermediate-risk patients, pembrolizumab plus axitinib and
26 nivolumab plus ipilimumab were associated with significantly higher improvement in
27 OS than sunitinib (HR 0.53, 95% CI 0.34-0.81; HR 0.66, 95% CI 0.50-0.87,
28 respectively)(Fig. 5B). For advanced/metastatic RCC of poor-risk, pembrolizumab
29 plus axitinib and nivolumab plus ipilimumab were significantly more efficacious for
30 OS than sunitinib (HR 0.43, 95% CI 0.23-0.80; HR 0.57, 95% CI 0.39-0.83,
31 respectively) (Fig. 5C). Based on the results of ranking, there were 81% and 78%
32 probabilities for pembrolizumab plus axitinib to be the best choice for intermediate-
33 and poor-risk patients, respectively (SUCRA =93.1% ; SUCRA= 91.4%, respectively)
34 (appendix Fig.1-3).
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51 3.4. Adverse events

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

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4 Fig. 6 and appendix Fig. 4 Stepwise comparison of all the seven therapies did not find
5 significant differences in rates of high-grade or overall adverse events. The most
6 common adverse events included diarrhea, hypertension, fatigue, and decreased
7 appetite.
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11 12 13 *3.5. Network assumptions, sensitivity analysis, publication bias, and risk of bias*

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

33 Our network meta-analysis of 15 RCTs including 8 995 individuals assessed the
34 efficacy and safety of all major systematic therapies for the treatment of
35 advanced/metastatic RCC in the first-line setting. Findings of this meta-analysis might
36 help to choose among systemic agents for the management of patients with previously
37 untreated advanced/metastatic RCC. In terms of PFS, avelumab plus axitinib was
38 most likely to be the best treatment regimen for advanced/metastatic RCC of
39 favorable-risk, and pembrolizumab plus axitinib seemed to be the most efficacious
40 treatment strategy for patients with intermediate- and poor-risk. In terms of OS, there
41 were no significant differences among systematic therapies for advanced/metastatic
42 RCC of favorable-risk, and pembrolizumab plus axitinib was probably to be the best
43 option for patients with intermediate- and poor-risk. In terms of drug-related adverse
44 events, there were no significant differences among systemic therapies.
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57 In RCC with clear cell subtype, hypoxia-inducible factor (HIF) accumulation due to
58 loss of von Hippel-Lindau (VHL) leads to overexpression of VEGF and platelet
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4 derived growth factor (PDGF), which promotes tumor angiogenesis [43 44]. This
5 process substantially makes a contribution to the development and progression of
6 clear cell RCC. Inhibiting the VEGF signaling has been supposed as the key
7 mechanism for antitumor effects in clear cell RCC. To date, eight targeted drugs have
8 been approved for treating advanced RCC: sunitinib, sorafenib, pazopanib,
9 cabozantinib, axitinib, everolimus, temsirolimus, and bevacizumab (in combination
10 with IFN- α).
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17 As shown in this analysis, for patients with intermediate-risk, sunitinib resulted in a
18 significant PFS benefit compared with everolimus. The varied clinical benefit could
19 be associated with mechanisms of action of TKI and mTOR inhibitor. Sunitinib not
20 only inhibit VEGF receptors -1, -2, and -3, which may be the most clearly relevant
21 targets in RCC so far, but also exhibit potent activity against PDGF receptor[11 45]. It
22 has been reported that PDGF plays a critical role in the recruitment of pericytes to
23 sprouting tumor vessels, and pericyte-covered vessels are more likely resistant to
24 anti-vascular therapy than those pericyte-negative vessels [46 47]. The mTOR
25 complex is the upstream of an intracellular signaling network regulating cell growth
26 and angiogenesis, and it plays a key role in the pathogenesis of advanced/metastatic
27 RCC [48]. It has been demonstrated that rapamycin analogs, including everolimus and
28 temsirolimus, inhibit only one of two signaling complexes of mTOR [49]. The
29 mTORC1 signaling is potently inhibited by everolimus and temsirolimus, while the
30 mTORC2 signaling is not [50]. Consequently, one downstream signaling of mTOR
31 activation is unopposed. The relatively unsatisfactory efficacy should disable the
32 mTOR inhibitors as more suitable therapies for the treatment of advanced/metastatic
33 RCC than TKIs. Regarding TKIs, our results suggest that sunitinib was most likely to
34 be the best treatment regimen for patients with favorable-risk disease.
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52 A potentially additive benefit from combinations of targeted drugs has been
53 suggested on the basis that they inhibit separate cellular pathways. However, our
54 results show that temsirolimus plus bevacizumab, and bevacizumab plus IFN- α
55 provide little survival benefit compared with sunitinib, further confirming absence of
56 evidence that combination treatment simultaneously inhibiting both VEGF and
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4 mTOR signaling results in therapeutic synergy [18 20 37].

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6 Immune checkpoint antibodies block the inhibitory T-cell receptor programmed
7 death-1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4)-signaling to augment
8 tumor specific immune response [51]. Nivolumab (an anti-PD-1 antibody) is
9 approved for the treatment of advanced RCC in the second line setting. Ipilimumab
10 (an anti-CTLA-4 antibody) is approved for the treatment of advanced melanoma.
11 Nivolumab plus ipilimumab has been reported significant efficacy in multiple tumor
12 types [52 53]. In this analysis, pembrolizumab plus axitinib appeared to be the
13 optimum treatment for intermediate- and poor-risk patients. Single-agent anti-tumor
14 activity of pembrolizumab and axitinib for mRCC has been reported in previous
15 studies [12 54]. Accordingly, axitinib in combination with pembrolizumab was
16 assessed and contributed to objective response rate in 73% patients in a phase 1b trial
17 [55]. Our result was consistent with results of KEYNOTE-426 trial, demonstrating
18 that pembrolizumab plus axitinib resulted in significant OS and PFS benefit compared
19 with sunitinib [39]. In addition, the survival benefit of pembrolizumab plus axitinib
20 was observed independent of PD-L1 status [39].

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35 Pembrolizumab plus axitinib is a combination of anti-PD-1 monoclonal antibody
36 and VEGF receptor TKI. Immune checkpoint inhibitors (ICI) block the inhibitory
37 T-cell receptor PD-1 or CTLA-4-signaling to augment tumor specific immune
38 response [51]. Besides of antiangiogenic effects, VEGF inhibition could enhance the
39 recruitment and infiltration of immune cells into the tumors [56 57]. It's reported that
40 simultaneous blockade of PD-1 and VEGF receptor-2 induced decreased tumor
41 neovascularization and tumor inhibition in a murine model [58]. These studies
42 suggested that the combination of ICI and VEGF receptor inhibitors could provide
43 enhanced benefit for mRCC. Recently, in addition to pembrolizumab plus axitinib,
44 avelumab (anti-PD-L1 antibody) plus axitinib, and atezolizumab (anti-PD-L1
45 antibody) plus bevacizumab were respectively assessed in two phase 3 RCTs
46 (IMmotion 151 and JAVELIN Renal 101), and both of them showed significant
47 survival benefit for mRCC compared with sunitinib [39 59]. However, there is no
48 head-to-head trial comparing combinations of ICI and VEGF receptor inhibitors
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4 inhibitors (pembrolizumab plus axitinib, aveluma plus axitinib, and atezolizumab plus
5 bevacizumab) directly. In consistent with our previous study, the present analysis
6 revealed that pembrolizumab plus axitinib presented the highest OS benefit for
7 intermediate- and poor-risk patients. For advanced/metastatic RCC of favorable-risk,
8 only avelumab plus axitinib was associated with a significantly higher improvement
9 in PFS than sunitinib, suggesting avelumab plus axitinib might be the optimum
10 treatment for favorable-risk patients. Considering patients continued to be followed
11 for OS in the JAVELIN Renal 101 trial [40], the real OS benefit for avelumab plus
12 axitinib over sunitinib requires additional follow-up.

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

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

9
10 However, the limitations of our study must be taken into account. The major
11
12 limitation of this network meta-analysis lies in the reporting quality of trials reviewed.
13
14 Ten included trials were not masked, which might affect the validity of our findings.
15
16 In addition, three included trials (CABOSUN, ROSORC, and RECORD-3) are phase
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18 2 RCTs with smaller sample size, and they may be less authoritative compared with
19
20 phase 3 RCTs. Moreover, most of the trials did not perform the analysis of OS in risk
21
22 subgroup, which made it impossible to assess the OS benefits of all the existing
23
24 treatments for different risk patients. In addition, this meta-analysis was conducted
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26 based on summary statistics rather than individual patient level data. There might be
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28 some confounding factors (*e.g.*, ethnic origin, prior nephrectomy, *etc.*) at the
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30 individual patient level that might influence the benefit of systemic treatments, but
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32 were not available; therefore analyses adjusted for these factors were impossible in
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34 our network meta-analysis. Access to patient-level longitudinal data would allow us to
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36 establish more robust and accurate conclusions in specific subgroups of patients.
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38 Moreover, the length of follow-up varied across studies, resulting in potential
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40 variations in survival benefits and adverse events. Due to only eight trials reporting
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42 median follow-up, sensitivity analyses adjusted for this factor were impossible.
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44 Moreover, individual dosage varied across studies and data were too sparse to
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46 investigate effects of different schedules, which might somewhat affect the
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48 generalisability of our findings. Since the analysis was based on highly selected RCTs
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50 and the results were based on fixed-effects models, findings in this analysis may not
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52 be entirely generalized to real-world practice. Finally, findings in this meta-analysis
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54 were mainly based on patients with clear-cell advanced RCC, thus no robust
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56 recommendations can be provided for non-clear-cell subtypes. Two trials included
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58 small subsets of non-clear-cell histotypes (11% and 14% of the study population),
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60 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.

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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.

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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)
Piccipio 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
Hanson 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;	59 (23-83)	71	27	67	7	12.7 (9.1-15.0)	0.756 (0.580-0.985)
	treatment-naive 181							
Sorafenib	257;	59 (23-85)	74	34	62	4	9.1 (7.3-10.8)	1 (Ref)
	treatment naive 181							
Sternberg 2010 (VEG105192)								
Pazopanib	290;	59 (28-82)	68	36	56	4	11.1	0.40 (0.27-0.60)
	treatment naive 155							
Placebo	n = 145;	62 (25-81)	74	40	51	6	2.8	1 (Ref)
	treatment naive 78							
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)
Ngqirier 2010 (TARGET)								
Sorafenib	451;	60	63.6	53.2	46.8	0	5.8	0.48 (0.32-0.73)
	treatment-naive 77							
Placebo	452;	60.5	69	45.2	54.8	0	2.8	1 (Ref)
	treatment-naive 84							
Rini 2010 (CALGB 90206)								

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4	Bevacizumab plus IFN- α	369	61 (56-70)	73	26	64	10	8.5 (7.5-9.7)	0.71 (0.61-0.83)	
5	IFN- α	363	62 (55-70)	66	26	64	10	5.2 (3.1-5.6)	1 (Ref)	
6	Escudier 2010 (AVOREN)									
7	Bevacizumab plus IFN- α	327	61 (30-82)	68	27	56	9	10.2	0.61 (0.51-0.73)	
8	IFN- α	322	60 (18-81)	73	29	56	8	5.4	1 (Ref)	
9										
10									Continued	
11	Molzer 2018 (CheckMate 214)									
12	Nivolumab plus Ipilimumab	550	62 (26-85)	75	23	61	17	11.6 (8.7-15.5)	0.82(0.64-1.05) [†]	
13	Sunitinib	546	62 (21-85)	72	23	61	16	8.4 (7.0-10.8)	1 (Ref)	
14	Choueiri 2017									
15										
16	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)	
17	Sunitinib	78	64(31-87)	73.1	0	80.8 [§]	19.2 [§]	5.6 (3.4 to 8.1)	1 (Ref)	
18										
19	Molzer 2019 (JAVELIN Renal 101)									
20	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)	
21	Sunitinib	444	61 (27-88)	77.5	22.5	66.0	10.1	8.4 (6.9-11.1)	1 (Ref)	
22										
23	Ronzi 2019 (KEYNOTE-426)									
24	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)	
25	Sunitinib	429	61 (26-90)	74.6	30.5 [§]	57.3 [§]	12.1 [§]	11.1 (8.7-12.5)	1 (Ref)	
26										

IFN- α = interferon- α ; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; CI = confidence interval; AE = adverse event; N/A = 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

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.

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4 The column treatment is compared with the row treatment. Odds ratios lower than 1
5 favor the column-defining treatment. Numbers in parentheses indicate 95% credible
6 intervals. SUN = sunitinib. PLA = placebo. SOR = sorafenib. PAZ = pazopanib. TIV
7 = tivozanib. CAB = cabozantinib. SOR_IL-2= sorafenib plus interleukin-2. NIV_IPI
8 = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI=
9 avelumab plus axitinib. Stepwise comparison of treatments did not find significant
10 differences in rates of high-grade adverse events.
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19 **Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis**
20 **for hazard ratios of progression-free survival**
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22 SUN = sunitinib. PLA = placebo. IFN = interferon- α . SOR = sorafenib. PAZ =
23 pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN =
24 bevacizumab plus interferon- α . TEM_BEV = temsirolimus plus bevacizumab.
25 NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib.
26 AVE_AXI= avelumab plus axitinib.
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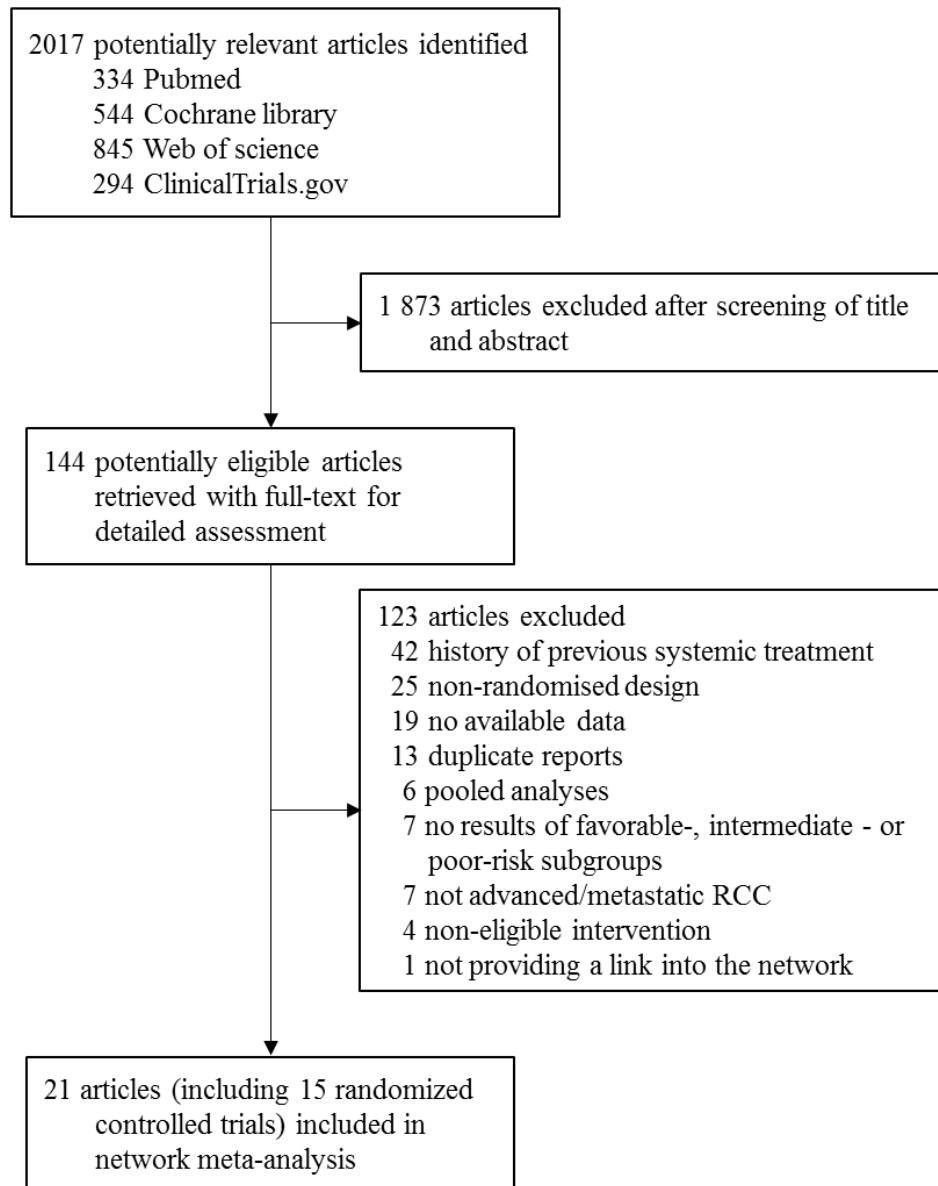


Fig. 1 - Literature search and selection

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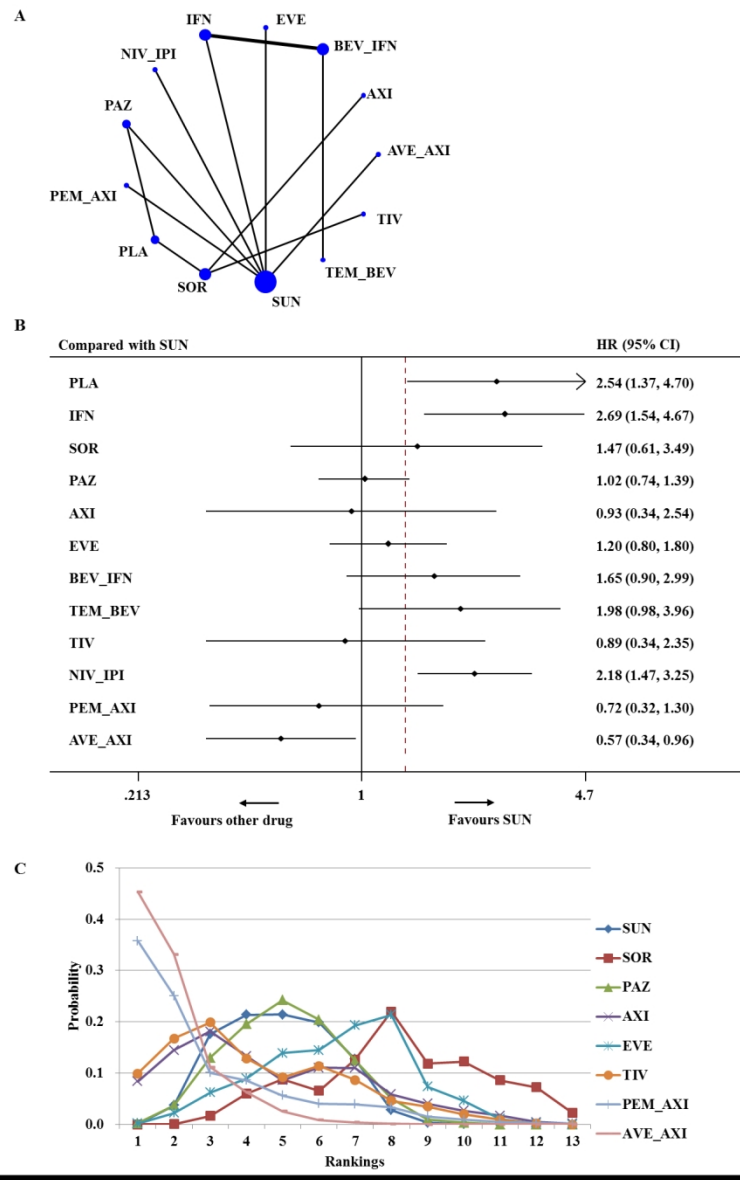


Fig. 2 - Analysis of progression-free survival for patients with favorable-risk disease. (A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) forest plot, with sunitinib as the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

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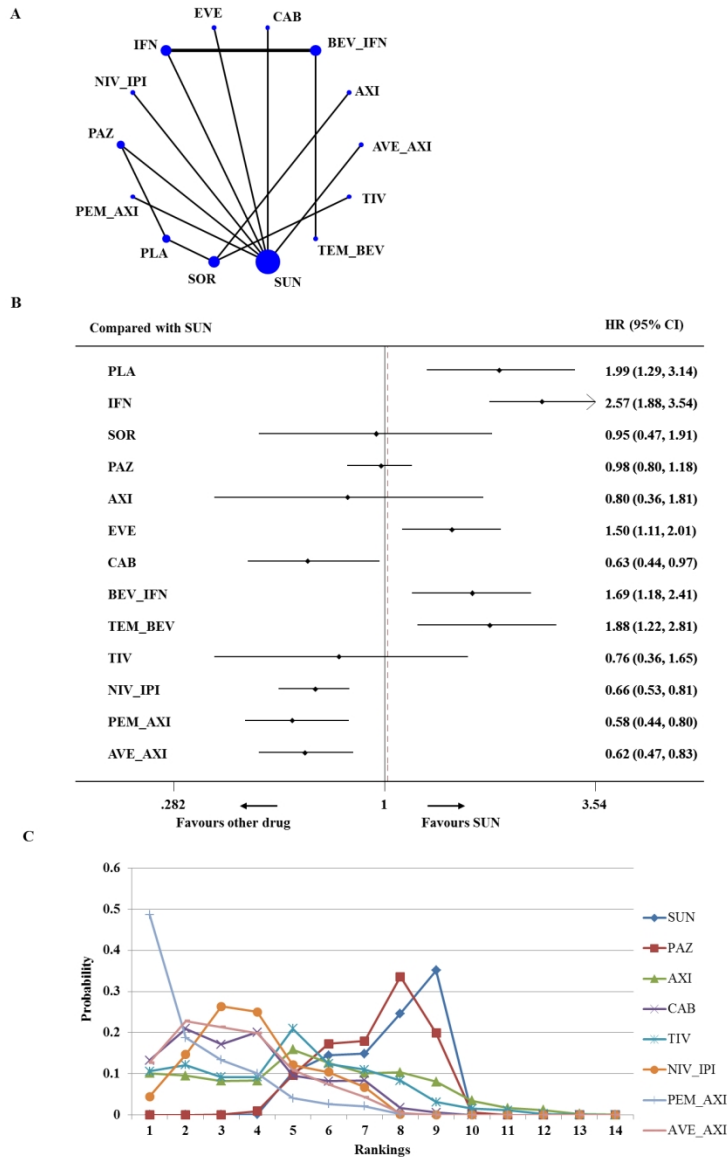


Fig. 3 - Analysis of progression-free survival for patients with intermediate-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. 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.

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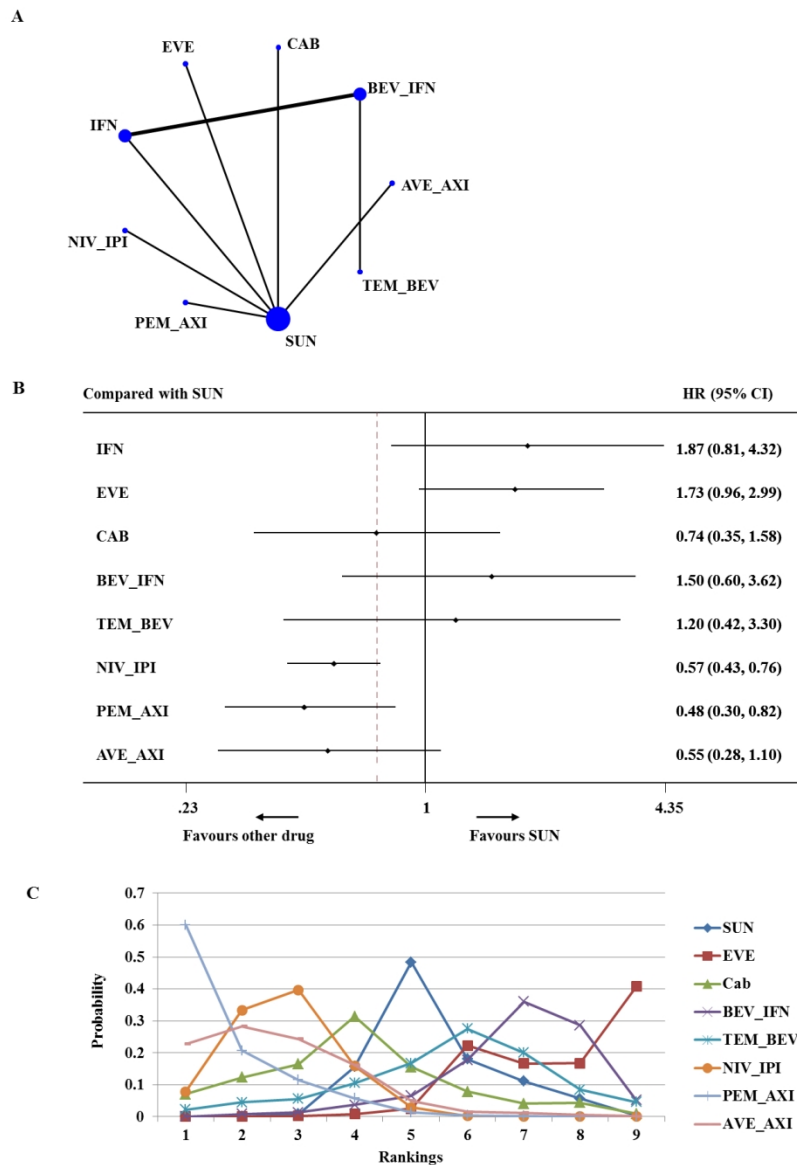


Fig. 4 - Analysis of progression-free survival for patients with poor-risk disease. (A) network diagram. (B) forest plot, with sunitinib as the comparator; (C) Ranking of treatments. HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. 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.

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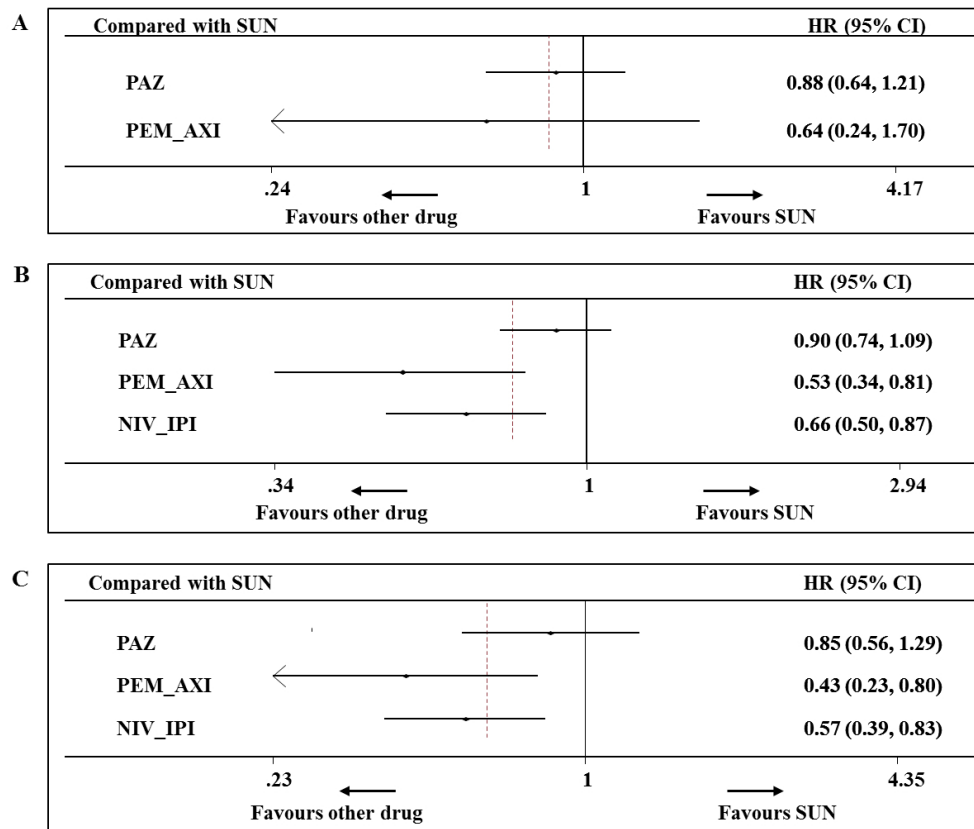


Fig.5- Analysis of overall survival for patients with favorable- risk (A), intermediate- risk (B), and poor-risk (C). HR = hazard ratio. CI = confidence interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. PAZ = pazopanib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab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

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SUN	0.40 (0.02, 8.55)	2.83 (0.06, 150.75)	1.07 (0.12, 9.19)	1.98 (0.02, 201.54)	0.92 (0.09, 8.13)	5.29 (0.06, 499.51)	0.49 (0.05, 4.26)	1.30 (0.15, 12.14)	1.00 (0.11, 8.77)
PLA		7.16 (0.63, 94.46)	2.67 (0.31, 24.54)	4.95 (0.20, 156.27)	2.30 (0.05, 99.17)	12.98 (0.45, 392.76)	1.24 (0.03, 52.88)	3.33 (0.08, 135.00)	2.48 (0.06, 109.18)
SOR			0.38 (0.01, 9.58)	0.69 (0.08, 6.50)	0.32 (0.00, 30.01)	1.82 (0.18, 16.55)	0.17 (0.00, 13.75)	0.46 (0.00, 39.97)	0.36 (0.00, 30.63)
PAZ				1.84 (0.04, 110.86)	0.87 (0.03, 19.18)	4.87 (0.09, 278.21)	0.46 (0.02, 10.04)	1.22 (0.06, 25.58)	0.92 (0.04, 19.41)
TIV					0.46 (0.00, 67.33)	2.63 (0.11, 53.00)	0.25 (0.00, 33.35)	0.66 (0.00, 91.27)	0.51 (0.00, 67.33)
CAB						5.80 (0.03, 947.65)	0.53 (0.02, 13.17)	1.42 (0.06, 33.89)	1.08 (0.05, 25.63)
SOR_IL-2							0.09 (0.00, 13.57)	0.25 (0.00, 40.53)	0.19 (0.00, 28.00)
NIV_IPI								2.65 (0.13, 58.75)	2.04 (0.09, 44.95)
PEM_AXI									0.76 (0.03, 16.68)
AVE_AXI									

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.

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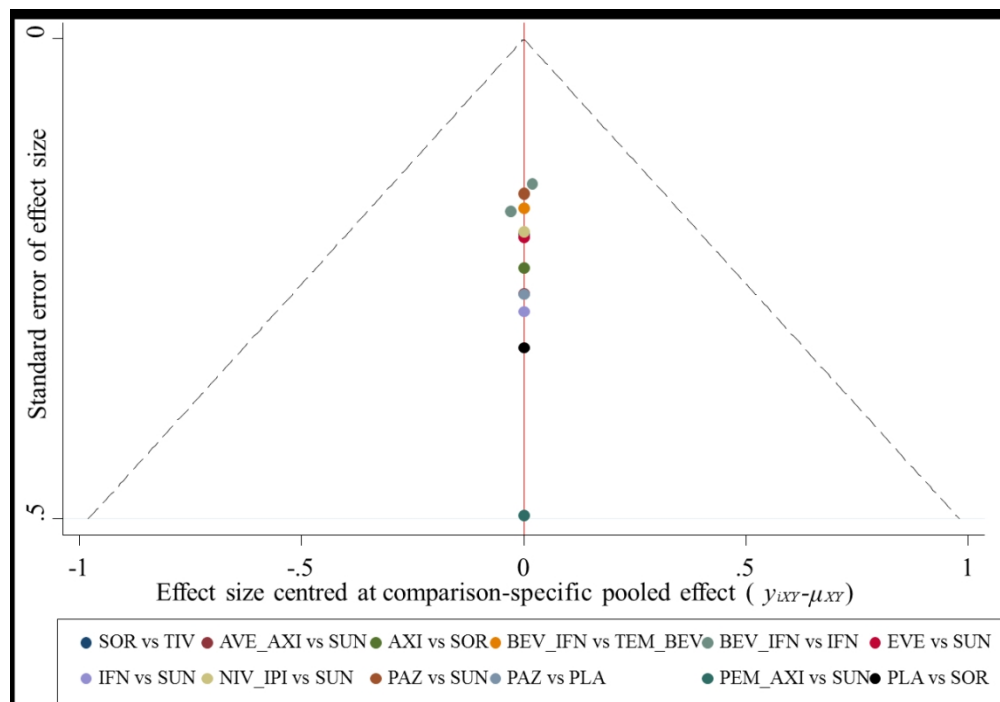


Fig. 7 - Funnel plot of randomized controlled trials included in the meta-analysis for hazard ratios of progression-free survival
 SUN = sunitinib. PLA = placebo. IFN = interferon- α . SOR = sorafenib. PAZ = pazopanib. AXI = axitinib. EVE = everolimus. TIV = tivozanib. BEV_IFN = bevacizumab plus interferon- α . TEM_BEV = temsirolimus plus bevacizumab. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI= pembrolizumab plus axitinib. AVE_AXI= avelumab plus axitinib.

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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 cabozantinib: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: (cabozantinib)) 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)
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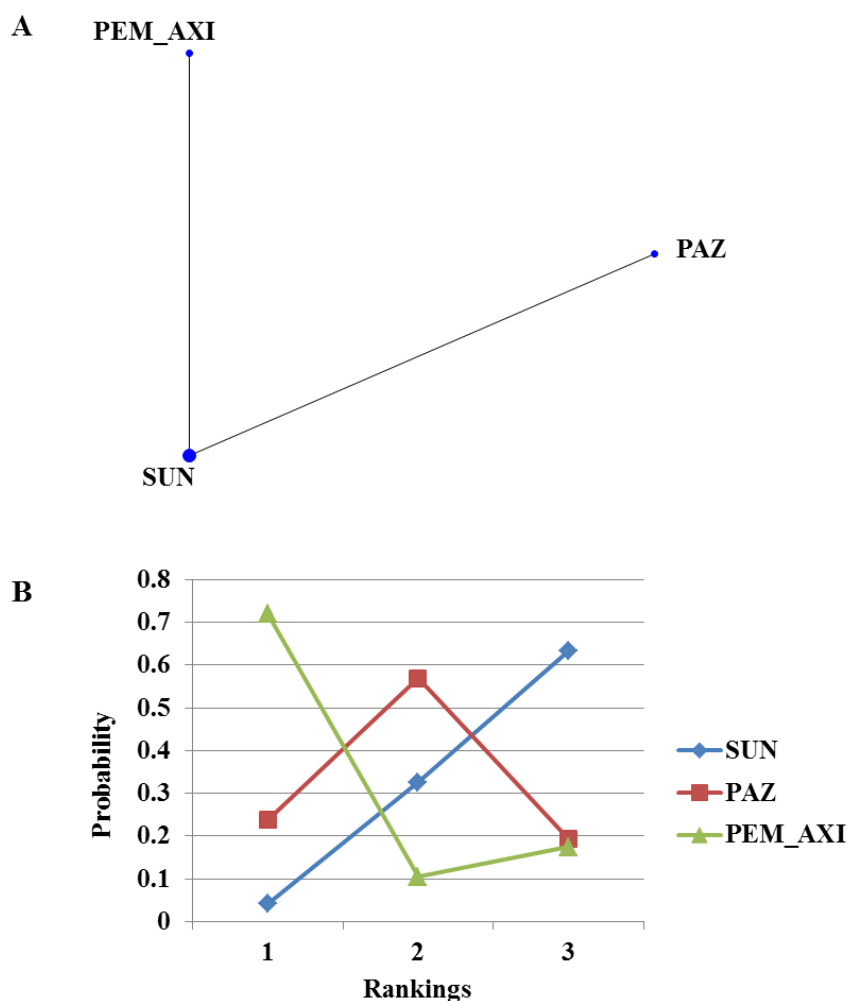
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5 Category: “renal cell carcinoma OR renal cancer OR renal carcinoma OR kidney cancer OR
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7 kidney carcinoma, Studies With Results”

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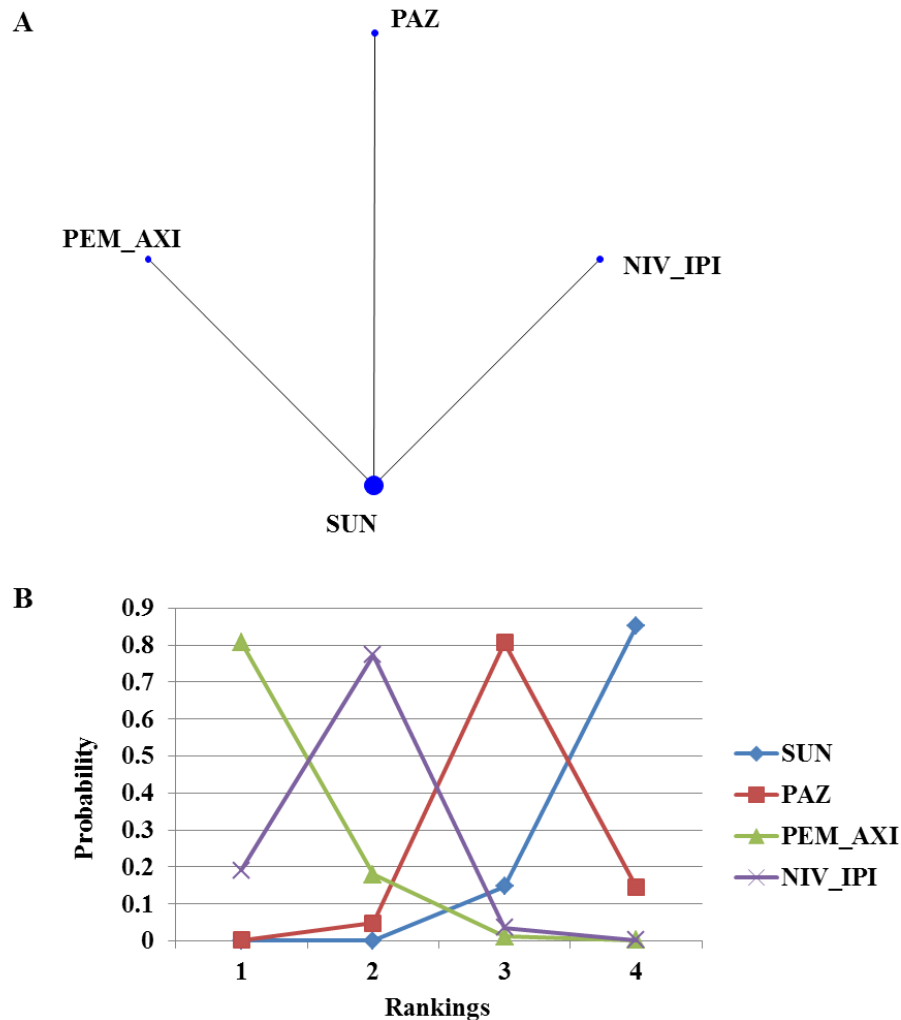
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Appendix figure 1 Analysis of overall survival for patients with favorable-risk disease.



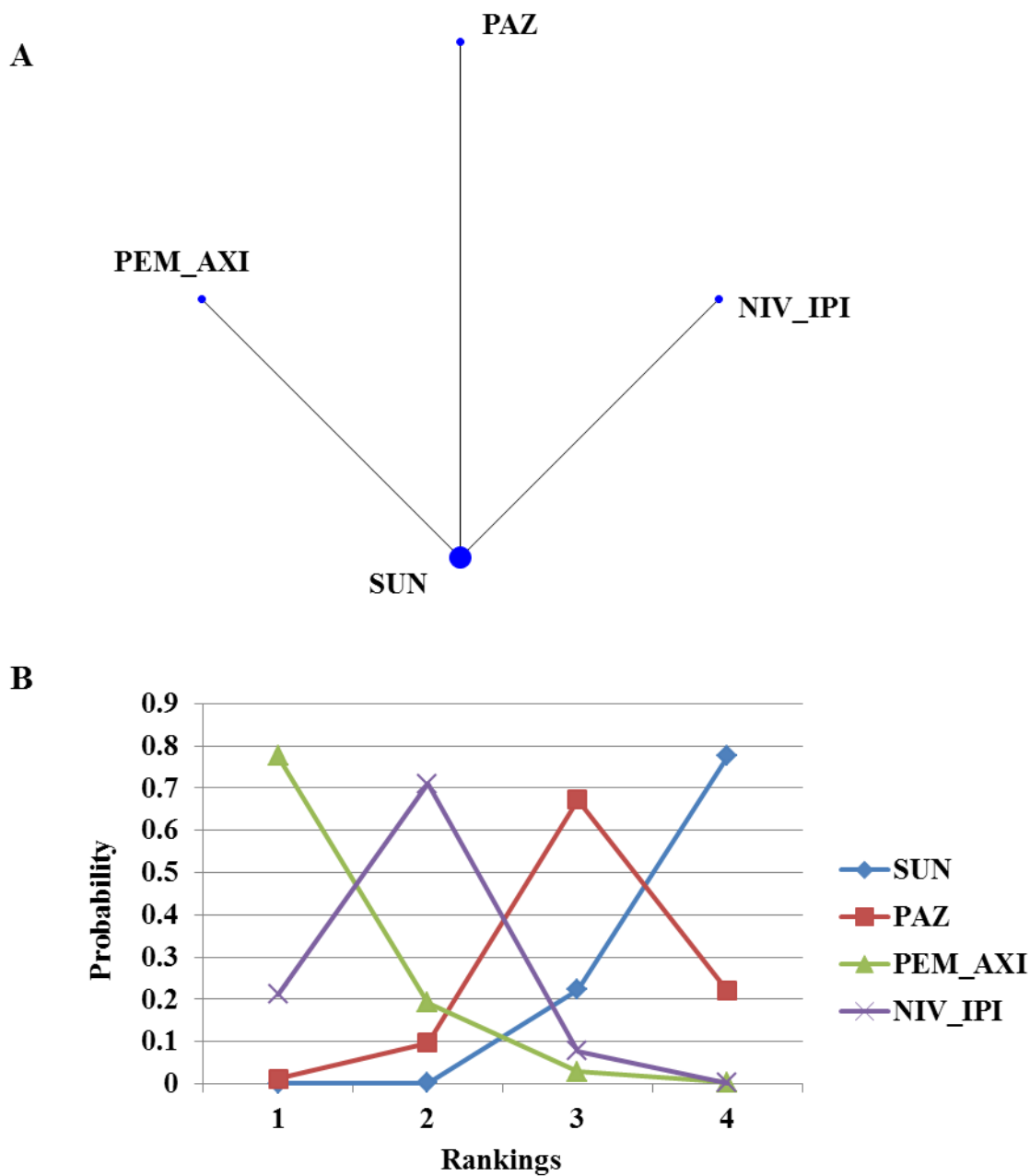
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. 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.



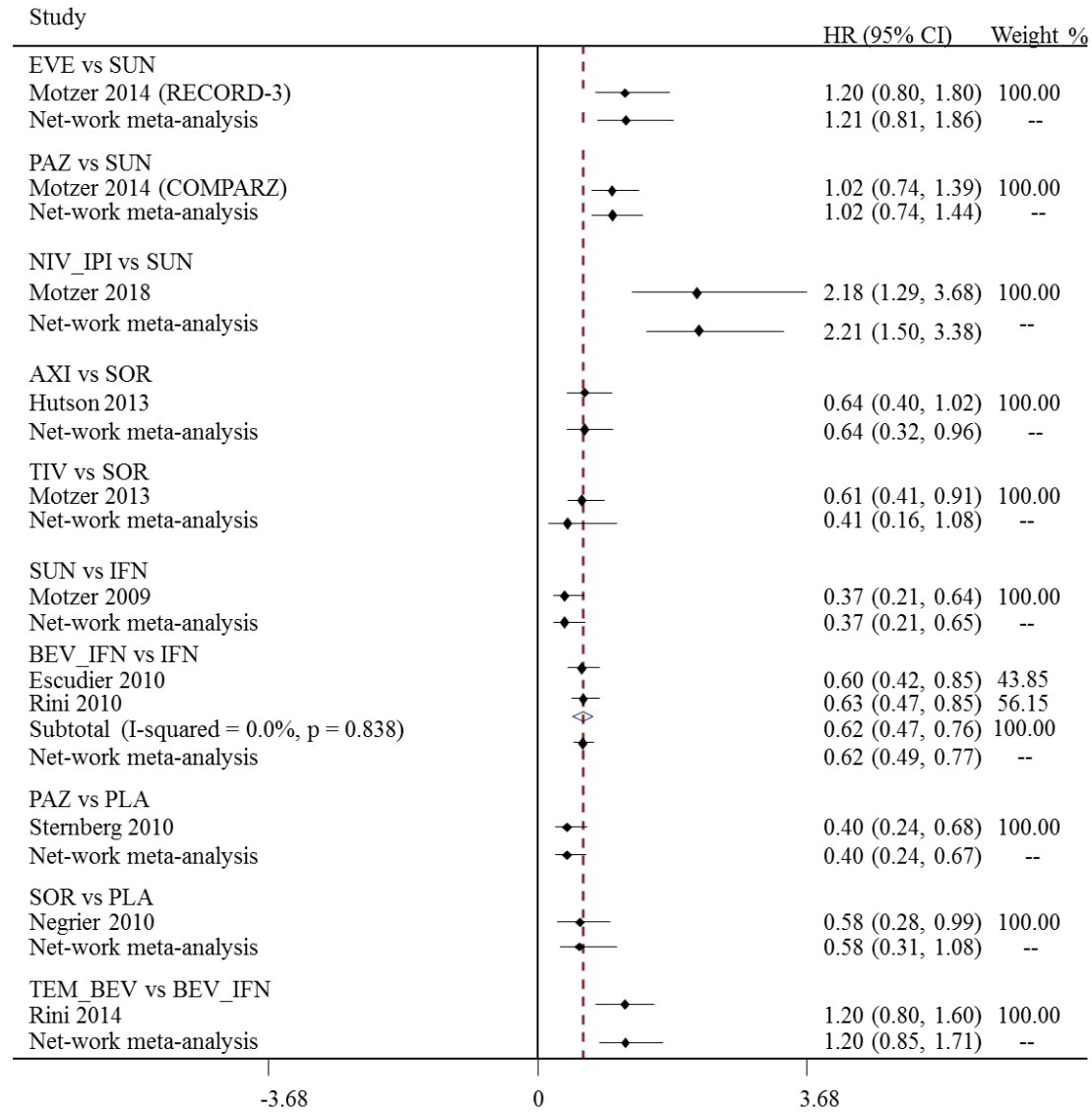
(A) network diagram: the size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. (B) Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. 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

SUN	2.28 (0.27, 23.95)	1.05 (0.03, 45.23)	0.34 (0.08, 1.40)	0.38 (0.05, 2.41)	1.61 (0.17, 19.17)
	PAZ	0.46 (0.01, 34.72)	0.15 (0.01, 1.94)	0.16 (0.01, 2.69)	0.68 (0.03, 18.38)
		CAB	0.33 (0.01, 14.72)	0.36 (0.00, 18.55)	1.57 (0.02, 115.31)
			NIV_IPI	1.12 (0.10, 11.68)	4.77 (0.32, 84.86)
				PEM_AXI	4.31 (0.22, 98.04)
					AVE_AXI

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Choueiri 2017	+	+	-	+	+	+	?
Escudier 2010 (AVOREN)	+	+	+	+	+	+	?
Hutson 2013	+	+	-	+	+	+	+
Motzer 2009	+	+	-	?	+	+	+
Motzer 2013	+	+	-	?	+	+	?
Motzer 2014 (COMPARZ)	+	+	-	?	+	+	+
Motzer 2014 (RECORD-3)	+	?	-	?	+	+	?
Motzer 2018 (CheckMate 214)	+	+	?	+	+	+	?
Motzer 2019 (JAVELIN Renal 101)	+	+	-	+	+	+	+
Negrier 2010 (TARGET)	+	+	+	+	+	+	+
Procopio 2013 (ROSORC)	+	+	-	-	+	+	?
Rini 2010 (CALGB 90206)	+	+	+	+	+	+	+
Rini 2014 (INTORACT)	+	+	-	+	+	+	+
Rini 2019 (KEYNOTE-426)	+	+	-	+	+	+	+
Sternberg 2010 (VEG105192)	+	+	+	+	+	+	?

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

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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

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