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Role of immune checkpoint inhibitor-based therapies for metastatic renal cell carcinoma in the first-line setting: A Bayesian network analysis

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ABSTRACT

Background: Several novel immune checkpoint inhibitor (ICI)-based treatments exhibited promising survival benefits for metastatic renal cell carcinoma (mRCC), yet there is no current guidance regarding the optimum first-line regimen. We performed this network analysis to compare the efficacy and safety of all available treatments for mRCC.

Methods: A systematic search of literature was conducted up to April 30, 2019, and the analysis was done on a Bayesian fixed-effect model.

Findings: Twenty-five randomized clinical trials (RCTs) involving 13,010 patients were included in this study. The results showed that for overall survival, pembrolizumab plus axitinib (hazard ratio [HR]: 0.53; 95% credible interval [CrI]: 0.38–0.73) and nivolumab plus ipilimumab (HR: 0.63; 95% CrI: 0.50–0.79) were significantly more effective than sunitinib, and pembrolizumab plus axitinib was probably (68%) to be the best choice. For progression-free survival, cabozantinib (HR: 0.66; 95% CrI: 0.46–0.94), pembrolizumab plus axitinib (HR: 0.69; 95% CrI: 0.57–0.84), avelumab plus axitinib (HR: 0.69; 95% CrI: 0.56–0.85), nivolumab plus ipilimumab (HR: 0.82; 95% CrI: 0.68–0.99), and atezolizumab plus bevacizumab (HR: 0.86; 95% CrI: 0.74–0.99) were statistically superior to sunitinib, and cabozantinib was likely (43%) to be the preferred options. Nivolumab plus ipilimumab (OR: 0.50; 95% CrI: 0.28–0.84), and atezolizumab plus bevacizumab (OR: 0.56; 95% CrI: 0.36–0.83) were associated with significantly lower rate of high-grade adverse events than sunitinib.

Interpretation: Our findings demonstrate that pembrolizumab plus axitinib might be the best treatment for mRCC, while nivolumab plus ipilimumab has the most favorable balance between efficacy and acceptability, and may provide new guidance to make treatment decisions.

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1. Introduction

Renal cell carcinoma (RCC) is one of the top ten most frequently diagnosed cancers in the world, accounting for approximately 90% of all adult renal malignancies [1]. It was estimated that 65,340 people would be diagnosed with, and 14,970 people would die of RCC in 2018 in the United States [2]. About 30% of patients with RCC present with metastatic tumors at the time of initial diagnosis typically require systemic treatment [3,4]. Targeted therapies with less toxicity and higher survival benefit have become the mainstay for metastatic RCC (mRCC) [5,6], and up till now, multiple targeted therapies such as tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin (mTOR) pathway inhibitors, and vascular endothelial growth factor (VEGF) monoclonal antibody in combination with interferon have been approved as first-line systemic treatments for mRCC [3].

With improved understanding of immune response to cancers, inhibition of immune checkpoints such as cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1) with monoclonal antibodies have been successfully used for treating solid tumors and haematological malignancies, and revolutionized the therapeutic strategy for cancers [7]. Thus, beyond targeted therapies, various immune checkpoint inhibitors (ICIs) have been tried as new first-line treatments for mRCC. Currently, combination of ICIs blocking PD-1 (nivolumab) and CTLA-4 (ipilimumab) was demonstrated to provide overall survival (OS) benefit for advanced RCC versus sunitinib in a phase 3 trial (CheckMate 214) [8]. Based on these data, nivolumab plus

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Research in context

Evidence before this study

Renal cell carcinoma (RCC) is one of the top ten most frequently diagnosed cancers in the world, accounting for approximately 90% of all adult renal malignancies. Era of immunotherapy for metastatic renal cell carcinoma (mRCC) has come. Recently, several immune checkpoint inhibitor (ICI)-based treatments were tested in clinical trials, and exhibited promising survival benefits, yet there has been no current guidance regarding the optimum regimen. Thus, the PubMed, Cochrane Library, Web of Science, and ClinicalTrials.gov were searched for articles up to April 30, 2019, to conduct a Bayesian network analysis, which may help to compare the efficacy and safety of the available first-line options for mRCC, and provide clinical guidance.

Added value of this study

To our knowledge, this study is the most comprehensive network analysis to assess the efficacy and safety of all available first-line systemic treatments for mRCC. This analysis is based on 25 randomized clinical trials (RCTs), which included 13,010 patients randomly assigned to 23 different systemic treatments.

Implications of all the available evidence

Our findings may provide new insights into different systemic treatments, especially the ICI-based treatments, which show that: pembrolizumab plus axitinib might be the best treatment for mRCC in the first-line setting; nivolumab plus ipilimumab had the most favorable balance between efficacy and acceptability; though cabozantinib was the most preferred option for progression-free survival (PFS), it was less effective than pembrolizumab plus axitinib and nivolumab plus ipilimumab for overall survival (OS), demonstrating ICI-based therapies have play an important role for treatment of mRCC. Evidence from our analysis may provide guidance to patients and clinicians when making treatment decisions and designing future comparative trials.

ipilimumab has been listed as a first-line treatment for RCC [9,10]. Moreover, in recent clinical trials (IMmotion151, KEYNOTE-426, and JAVELIN Renal101), other ICI-based combination treatments including atezolizumab plus bevacizumab, pembrolizumab plus axitinib, and avelumab plus axitinib also exhibited significantly OS or progression-free survival (PFS) benefit for mRCC than sunitinib [11–13].

Obviously, the era of immune checkpoint therapy has come. However it is difficult for clinicians to identify the optimum treatment since existing head-to-head randomized clinical trials (RCTs) are insufficient to simultaneously compare the ICI-based related therapies and conventional first-line therapies for mRCC in terms of effectiveness and safety. Therefore, we sought to summarize, and compare the clinical outcomes and adverse events (AEs) associated with all the available first-line options for mRCC using the Bayesian network analysis.

2. Materials and methods

2.1. Data sources and search strategy

This study was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement for network meta-analysis [14]. A systematic search of literature was conducted on PubMed, Cochrane Library, Web of Science, and ClinicalTrials.gov for RCTs comparing at least two first-line systemic therapies of mRCC in April 2019. All the identified trials and relevant reviews were screened to ensure completeness. No publication date or language restrictions were imposed. The complete search terms and systematic search strategy are documented in Appendix 1 in Supplementary material.

2.2. Selection criteria

Inclusion of studies was restricted to RCTs. Patients with mRCC received systemic therapies were considered. Relevant interventions included, but were not restricted to: sunitinib, cabozantinib, pazopanib, atezolizumab, temsirolimus, tivozanib, nintedanib, everolimus, axitinib, sorafenib, nivolumab plus ipilimumab, pembrolizumab plus axitinib, avelumab plus axitinib, atezolizumab plus bevacizumab, bevacizumab plus IFN-α. Trials were excluded if patients were assigned to placebo or observation, or had previously received systemic therapy. Nonoriginal, duplicates, and non-RCT designs were not permitted. Firstly, we screened the titles and abstracts of the studies which were obtained through the systematic search, and excluded the studies if they satisfied the following criteria: (1) duplicates; (2) non-RCT designs including animal/cell experiments, case reports, cohort/case-control studies, which could be identified through titles and abstracts; (3) clinical trials which contained less than two systemic therapies. Subsequently, the remaining studies were given a full-text review, and further exclusions were made if they met the following exclusion criteria: (1) initial or duplicate reports; (2) reviews and editorials; (3) pooled analyses; (4) non-randomized clinical trials; (5) clinical trials of second-line treatments; (6) clinical trials not including active comparator arm. After the full-text review, the eligible RCTs were included in our study and utilized for further analyses.

2.3. Outcomes

The primary outcome was OS. PFS and high-grade (grade ≥ 3) drug-related AEs (National Cancer Institute Common Toxicity Criteria version 3.0) were assessed as the secondary outcomes.

2.4. Data extraction and quality assessment

Search and screening of the potentially relevant studies at the title and abstract level were independently performed by two reviewers (Junpeng Wang and Xin Li). Full-texts were reviewed when abstracts were insufficient to assess the eligibility of identified trials. Subsequently, data on patient characteristics, treatment strategies, definition of outcomes, and numbers of events were extracted into a standardized form by one author (Junpeng Wang), and verified by another author (Xin Li). Disagreements were resolved by consensus in consultation with a third reviewer (Xiaoqiang Wu). The methodological quality of included RCTs was assessed using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials [15].

2.5. Data synthesis and analysis

In the pooled analysis, both random-effect model and fixed-effect model were performed with Bayesian approach [16]. For the assessment of OS and PFS, the relevant outcomes were presented as the published hazard ratios (HRs) with 95% credible intervals (CrIs) [17]. For studies not reporting HRs, we calculated them employing the pragmatic approach reported by Tierney et al. [18]. When assessing drug-related AEs, odds ratios (ORs) were estimated for meta-analysis using the available raw data abstracted from the trials [17]. For the assessment of OS and PFS, contrast-based approach was applied. The results were obtained from a run of 15,000 iterations (3 chains, 5000 per chain), after a training phase of 5000 iterations. In order to minimize autocorrelation, we applied a thinning interval of 50 for each chain. Detailed operation

code was available in Appendix 2 in Supplementary material. For high-grade AEs, we computed ORs on averages of the 60,000 iterations after a training phase of 40,000 iterations. The treatments were ranked in terms of OS, PFS and high-grade AEs, respectively, using the distribution of the ranking probabilities and the surface under the cumulative ranking curve (SUCRA) [19].

Network plots were utilized to illustrate the connectivity of the treatment networks in terms of OS, PFS and high-grade AEs, respectively. Heterogeneity in the network was quantified using the chi-square test and I^2 statistic within each pairwise comparison when 2 or more trials were available for the comparison. When p value < .10 and I^2 > 50%, heterogeneity was considered to be fairly high [20]. Model fit was assessed based on the deviance information criteria (DIC) and between-study standard deviation [16,21,22]. Differences of DIC values between the models of >3 or 5 were considered significant [16,23]. Since one of the key assumptions behind network meta-analysis is that direct and indirect evidence on the same comparisons do not disagree beyond chance (ie, consistency), network inconsistencies should be considered [16]. In our networks, most of the direct comparisons were provided by only one trial, and it was uncommon for most comparisons to have both direct and indirect evidence, thus we assumed coherence for our analysis. Node-splitting approach was performed to detect if there was incoherence in closed loop [16]. Transitivity assumption (i.e., trials comparing different treatments are similar in terms of important characteristics) was evaluated by comparing distribution of potential effect modifiers across the available trials [24]. We considered median age and sex ratio of the patients as the effect modifiers. Sensitivity analyses were performed excluding studies with performance bias, with detection bias, that selected non-clear cell carcinoma subtype, and that were randomized phase 2 trials, respectively. All the data analyses except the assessment of OR were performed using OpenBUGS version 3.2.2, and the results were visualized with Stata v.12 (StataCorp, College Station, TX, USA) for nice graphics. We analyzed OR using GeMTC to reduce analysis time and efforts, since it didn't require manually writing a statistical model [25].

3. Results

3.1. Search results, study characteristics and network assumption

Through literature search, 2390 potentially eligible studies were identified, of which 2294 were excluded based on screening titles and abstracts (Fig. 1). After a full-text review of 96 remaining studies, 25 unique RCTs (13,010 patients) were included in this network meta-analysis (Table 1). In the included trails, 23 first-line systemic treatments were involved. All treatments were assessed in at least one RCT. The mean sample size was 218 patients per group (range 32–557), and seven RCTs having at least 100 patients per group. Twenty two trials were selected for clear-cell carcinoma subtypes [11–13,26–34], and three trials also included small subsets of non-clear-cell histotypes, each comprising 4%–15% of the study population [35–37]. Details of RCT characteristics were summarized in Table 1. There was no evidence that median age and sex ratio differed across the trials (Supplementary Figs. S1 and S2). No major differences in study characteristics were observed. The included patients with a median age of 61 years were prevalently male (72.3%, 6033 of 8341). The networks of eligible comparisons were graphically represented in network plots, showing that there were 15, 23 and 20 treatments connected to at least one other treatment in terms of OS (Fig. 2A), PFS (Fig. 2B) and high-grade AEs (Fig. 2C), respectively.

In our analysis, DIC values (or between-study standard deviation values for OR) of fixed-effect model were lower than that of random-effect model (Supplementary Tables S1–S3) without significance. Since most of the direct comparisons were informed by a single trial, heterogeneity was driven entirely by few direct comparisons with 2 or more trials, and was found to be very low (I^2 < 50%, Supplementary Table S4). Therefore, based on both of DIC and heterogeneity, the fixed-effect was selected as the appropriate fit. Results of random-effect model could be found in Supplementary material. An extended description of the assessment of network inconsistency was noted in the Supplementary Table S5, showing that there was no incoherence.

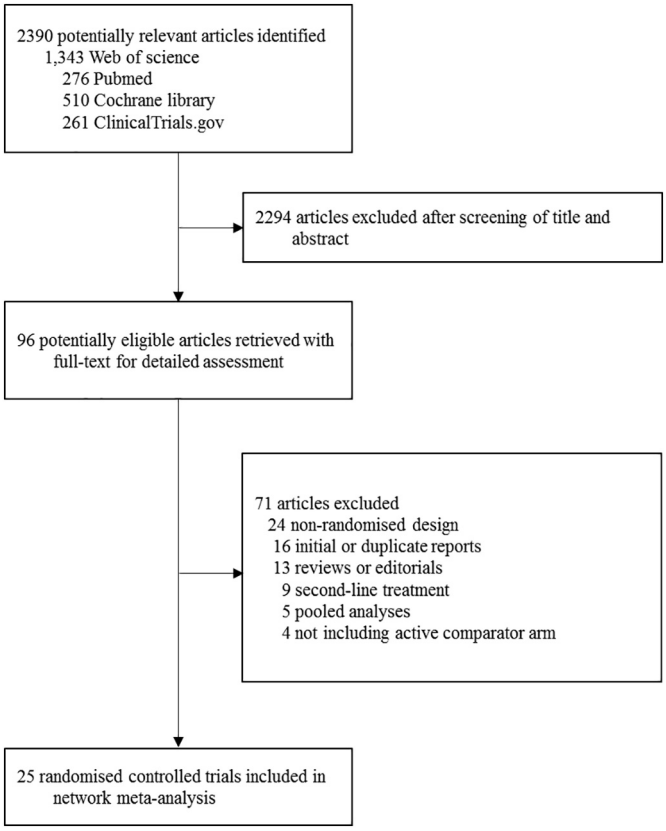

Fig. 1. Literature search and selection.

3.2. Overall survival

Totally, 15 first-line systemic treatments presented in 16 studies (9343 patients) were analyzed for OS [11–13,26,30–34,36,38–43]. The network meta-analysis demonstrated that pembrolizumab plus axitinib (HR: 0.53; 95% CrI: 0.38–0.73), and nivolumab plus ipilimumab (HR: 0.63; 95% CrI: 0.50–0.79) were associated with significantly higher improvement in OS than sunitinib (Fig. 3A). Most treatments (9/14) were associated with significantly higher risks of over mortality compared with pembrolizumab plus axitinib, except cabozantinib (HR: 1.52; 95% CrI: 0.86–2.67), nivolumab plus ipilimumab (HR: 1.19; 95% CrI: 0.80–1.76), avelumab plus axitinib (HR: 1.47; 95% CrI: 0.91–2.35), pazopanib plus everolimus (HR: 1.57; 95% CrI: 0.80–3.06), and nivolumab (HR: 1.74; 95% CrI: 0.93–3.26) (Fig. 3B). Based on the results of ranking, there was a 68% probability for pembrolizumab plus axitinib to be the best choice for OS (SUCRA = 96.3%), while IFN-α was likely to be the worst (Fig. 6 and Supplementary Table S6).

3.3. Progression-free survival

In terms of PFS, 25 trials (11,771 patients) comparing 23 first-line systemic treatments were available for assessment [11–13,26–47]. According to the results, cabozantinib (HR: 0.66; 95% CrI: 0.46–0.94), nivolumab plus ipilimumab (HR: 0.82; 95% CrI: 0.68–0.99), pembrolizumab plus axitinib (HR: 0.69; 95% CrI: 0.57–0.84), avelumab plus axitinib (HR: 0.69; 95% CrI: 0.56–0.85), and atezolizumab plus bevacizumab (HR: 0.86; 95% CrI: 0.74–0.99) were statistically superior

Table 1
Studies included in the multiple-treatments meta-analysis.

Study	Number of patients	Age (years) median (range)	Sex (% male)	Median PFS in months	PFS HR (95% CrI)	Median OS in months	OS HR (95% CrI)	High grade AE, %	Phase of the clinical trial
Rini 2019 (KEYNOTE-426)									
Pembrolizumab plus axitinib	432	62 (30–89)	308 (71)	15.1	0.69 (0.57–0.84)	NR	0.53 (0.38–0.74)	76	3
Sunitinib	429	61 (26–90)	320 (75)	11.1	1 (Ref)	NR	1 (Ref)	71	
Motzer 2019 (JAVELIN Renal 101)									
Avelumab plus axitinib	442	62 (29–83)	316 (72)	13.8	0.69 (0.56–0.84)	NR	0.78 (0.55–1.08)	71	3
Sunitinib	444	61 (27–88)	344 (78)	8.4	1 (Ref)	NR	1 (Ref)	72	
Motzer 2018 (CheckMate 214)									
Nivolumab plus ipilimumab	550	62 (26–85)	413 (75)	11.6	0.82(0.64–1.05)[‡]	NR	0.63 (0.44–0.89) §	46	3
Sunitinib	546	62 (21–85)	395 (72)	8.4	1 (Ref)	26	1 (Ref)	63	
Motzer 2018 (IMmotion 151)									
Atezolizumab plus bevacizumab	454	62 (24–88)	318 (70)	11.2	0.83 (0.70–0.97)	NR	0.81 (0.63–1.03)	40	3
Sunitinib	461	60 (18–84)	350 (76)	8.4	1 (Ref)	NR	1 (Ref)	54	
Tomita 2017									
Sunitinib	57	NA	NA	8.7	0.67 (0.42–1.08)	NA	NA	NA	3
Sorafenib	63	NA	NA	7	1 (Ref)	NA	NA	NA	
McDermott 2017 (IMmotion150)									
Atezolizumab plus bevacizumab	101	NA	NA	11.7	1.00 (0.69–1.45)	NA	NA	40	2
Atezolizumab	103	NA	NA	6.1	1.19 (0.8–1.71)	NA	NA	16	
Sunitinib	101	NA	NA	8.4	1 (Ref)	NA	NA	56	
Cirkel 2017 (ROPETAR)									
Pazopanib plus everolimus	52	65 (44–87)	38 (73)	7.4	0.81 (0.50–1.29)	35	0.90 (0.51–1.58)	42	2
Pazopanib	49	67 (38–82)	31 (63)	9.4	1 (Ref)	18.5	1 (Ref)	49	
Choueiri 2017 (CABOSUN)									
Cabozantinib	79	63 (40–82) 82.0)	66 (84)	8.2	0.66 (0.46 to 0.95)	30.3	0.8 (0.50 to 1.26)	67	2
Sunitinib	78	64 (31–87)	57 (73)	5.6	1 (Ref)	21.8	1 (Ref)	68	
Ravaud 2015 (RECORD-2)									
Everolimus plus bevacizumab	182	60 (20–84)	138 (76)	9.3	0.91 (0.69–1.19)	27.1	1.01 (0.75–1.34)	81	2
Bevacizumab plus interferon-α	183	60 (31–81)	131 (72)	10	1 (Ref)	27.1	1 (Ref)	76	
Eisen 2015									
Nintedanib	64	62 (42–86)	44 (69)	8.44	1.12 (0.70–1.80)	20.37	0.92 (0.54–1.56)	48	2
Sunitinib	32	58 (29–79)	22 (69)	8.83	1 (Ref)	21.22	1 (Ref)	59	
Eichelberg 2015 (SWITCH)									
Sorafenib	182	64 (39–84)	139 (76)	5.9	1.19(0.97–1.47)[†]	NA	NA	64	3
Sunitinib	183	65 (40–83)	135 (74)	8.5	1 (Ref)	NA	NA	65	
Rini 2014 (INTORACT)									
Temsirolimus plus bevacizumab	400	59 (22–87)	288 (72)	9.1	1.1(0.9–1.3)	25.8	1.0 (0.9–1.3)	80	3
Bevacizumab plus interferon-α	391	58 (23–81)	270 (69)	9.3	1 (Ref)	25.5	1 (Ref)	76	
Motzer 2014 (RECORD-3)									
Everolimus	238	62 (20–89)	166 (70)	7.9	1.4 (1.2–1.8)	NA	NA	NA	2
Sunitinib	238	62 (29–84)	176 (74)	10.7	1 (Ref)	NA	NA	NA	
Motzer 2013									
Tivozanib	181	59 (23–83)	185 (71)	12.7	0.756 (0.580–0.985)	28.8	NA	61	3
Sorafenib	181	59 (23–85)	189 (74)	9.1	1 (Ref)	29.3	NA	70	
Motzer 2013 (COMPARZ)									
Pazopanib	557	61 (18–88)	398 (71)	8.4	1.05 (0.90–1.22)	28.4	0.91 (0.76 to 1.08)	74	3
Sunitinib	553	62 (23–86)	415 (75)	9.5	1 (Ref)	29.3	1 (Ref)	73	
Hutson 2013									
Axitinib	192	58 (23–83)	134 (70)	10·1	0.77 (0.56–1.05)	NA	NA	33	3
Sorafenib	96	58 (20–77)	74 (77)	6.5	1 (Ref)	NA	NA	25	
Rini 2012									
Sorafenib plus trebananib (10 mg/kg)	50	60 (39–80)	50 (82)	9	0.80 (0.50–1.28)	NR	NA	66	2
Sorafenib plus trebananib (3 mg/kg)	51	58 (28–84)	51 (69)	8.5	0.96 (0.61–1.50)	29.2	NA	73	
Sorafenib plus placebo	51	59 (38–84)	51 (75)	9	1 (Ref)	27.1	NA	86	
Procopio 2011 (ROSORC)									
Sorafenib plus interleukin-2	66	64 (57–69)[*]	52 (79)	NA	0.91 (0.62–1.35)[#]	38	0.91 (0.59–1.41)	38	2
Sorafenib	62	62 (52–69)[*]	43 (69)	NA	1 (Ref)	33	1 (Ref)	26	
Negrier 2011 (TORAVA)									
Temsirolimus plus bevacizumab	88	62.0 (33–83)	65 (74)	8.2	0.95 (0.62–1.45)[#]	NA	NA	NA	2
Bevacizumab plus interferon-α	41	61.9 (40–79)	27 (66)	16.8	0.65 (0.34–1.24)[#]	NA	NA	NA	
Sunitinib	42	61.2 (33–83)	32 (76)	8.2	1 (Ref)	NA	NA	NA	

(continued on next page)

Table 1 (*continued*)

Study	Number of patients	Age (years) median (range)	Sex (% male)	Median PFS in months	PFS HR (95% CrI)	Median OS in months	OS HR (95% CrI)	High grade AE, %	Phase of the clinical trial
Jonasch 2010									
Sorafenib plus interferon-α	40	60.7 (43–81)	29 (73)	7.56	0.85 (0.51–1.42)	27.04	2.17 (0.92–5.12)	NA	2
Sorafenib	40	62.4 (45–83)	32 (80)	7.39	1 (Ref)	NR	1 (Ref)	NA	
Motzer 2009									
Sunitinib	375	62 (27–87)	267 (71)	11	0.54 (0.45–0.64)	26.4	0.81 (0.66–0.99)	NA	3
Interferon-α	375	59 (34–85)	269 (72)	5	1 (Ref)	21.8	1 (Ref)	NA	
Escudier 2009									
Sorafenib	97	62.0 (34–78)	65 (67)	5.7	0.88 (0.61–1.27)	NA	NA	41	2
Interferon-α	92	62.5 (18–80)	52 (57)	5.6	1 (Ref)	NA	NA	36	
Rini 2008 (CALGB 90206)									
Bevacizumab plus interferon-α	369	61 (56–70)	269 (73)	8.5	0.71 (0.61–0.83)	18.3	0.86 (0.73–1.01)	80	3
Interferon-α	363	62 (55–70)	239 (66)	5.2	1 (Ref)	17.4	1 (Ref)	63	
Hudes 2007 (ARCC)									
Temsirolimus	209	58 (32–81)	139 (66)	5.5	0.82 (0.64–1.06)[#]	10.9	0.73 (0.58 to 0.92)	67	3
Temsirolimus plus interferon-α	210	59 (32–82)	145 (69)	4.7	0.74 (0.61–0.89)[#]	8.4	0.96 (0.76 to 1.20)	78	
Interferon-α	207	60 (23–86)	148 (71)	3.1	1 (Ref)	7.3	1 (Ref)	84	
Escudier 2007 (AVOREN)									
Bevacizumab plus interferon-α	327	61 (30–82)	222 (68)	10.2	0·61 (0·51–0·73)	23.3	0.78 (0.63 to 0.96)	60	3
Interferon-α	322	60 (18–81)	234 (73)	5.4	1 (Ref)	21.3	1 (Ref)	45	

IFN = interferon-α; PFS = progression-free survival; OS = overall survival; HR = hazard ratio; CrI = credible intervals; AE = adverse event;
NA = not available; NR = not reached; Ref = reference group (hence hazard ratio set to 1);
* Interquartile range.
† 90% CrI; ǂ 99.1% CrI; § 99.8% CrI.

to sunitinib, while temsirolimus (HR: 1.38; 95% CrI: 1.03–1.85), everolimus (HR: 1.40; 95% CrI: 1.14–1.71), sorafenib (HR: 1.31; 95% CrI: 1.08–1.59), and IFN-α (HR: 1.68; 95% CrI: 1.44–1.96) were statistically inferior to sunitinib (Fig. 4A). Compared with pembrolizumab plus axitinib, pazopanib (HR: 1.53; 95% CrI: 1.19–1.94), atezolizumab (HR: 1.73; 95% CrI: 1.13–2.64), temsirolimus (HR: 2.00; 95% CrI: 1.41–2.83), everolimus (HR: 2.03; 95% CrI: 1.53–2.68), sorafenib (HR: 1.90; 95% CrI: 1.44–2.49), IFN-α (HR: 2.44; 95% CrI: 1.91–3.12), temsirolimus plus bevacizumab (HR: 1.67; 95% CrI: 1.24–2.24), temsirolimus plus IFN-α (HR: 1.80; 95% CrI: 1.32–2.46), bevacizumab plus IFN-α (HR: 1.57; 95% CrI: 1.21–2.04), sorafenib plus trebanbanib (HR: 1.66; 95% CrI: 1.08–2.55), and sorafenib plus IL-2 (HR: 1.73; 95% CrI: 1.07–2.77) were statistically inferior (Fig. 4B). None of the treatments had significantly better efficacies than pembrolizumab plus axitinib (Fig. 4B). Ranking on PFS indicated that cabozantinib had the highest probability (43%) to be the preferred options (SUCRA = 92.5%), followed by pembrolizumab plus axitinib, and avelumab plus axitinib (Supplementary Fig. S3 and Supplementary Table S7).

3.4. High-grade adverse events

Toxicity of the treatments based on high-grade AEs within 20 RCTs (10,345 patients) were analyzed, and the results of comparisons caused by 20 systemic treatments are presented in Fig. 5 [11–13,26,28–34,36–38,44–46]. Compared with sunitinib, atezolizumab (OR: 0.15; 95% CrI: 0.07–0.30), temsirolimus (OR: 0.24; 95% CrI: 0.09–0.69), nivolumab plus ipilimumab (OR: 0.50; 95% CrI: 0.28–0.84), atezolizumab plus bevacizumab (OR: 0.56; 95% CrI: 0.36–0.83), and sorafenib plus trebanbanib (OR: 0.32; 95% CrI: 0.10–0.97) were associated with significantly lower rate of high-grade AEs. Pazopanib (OR: 2.10; 95% CrI: 1.00–4.67), pembrolizumab plus axitinib (OR: 2.60; 95% CrI: 1.25–5.64), everolimus plus bevacizumab (OR: 4.38; 95% CrI: 1.42–13.28), temsirolimus plus bevacizumab (OR: 4.37; 95% CrI: 1.83–10.84), bevacizumab plus IFN-α (OR: 3.37; 95% CrI: 1.39–8.41), and sorafenib plus IL-2 (OR: 3.36; 95% CrI: 1.09–12.25) showed statistically higher incidences of high-grade AEs than nivolumab plus ipilimumab. Among all analyzed treatments, atezolizumab and temsirolimus had the highest probability to be the best tolerated among all analyzed treatments (SUCRA = 97.2% and 91.8%, respectively), whereas temsirolimus plus bevacizumab everolimus and plus bevacizumab had the least favorable toxicity profile (Supplementary Fig. S4 and Table S8).

3.5. Sensitivity analysis, publication bias, and risk of bias

To test the robustness of significant results, we conducted sensitivity analyses excluding studies with performance bias, with detection bias, that selected non-clear cell carcinoma subtype, and that were randomized phase 2 trials on OS, PFS and high AEs. The results showed that removing these studies did not substantially affect the results (Supplementary Tables S9–20), indicating the robustness of our findings. The comparison-adjusted funnel plot for OS reported a symmetric distribution (Supplementary Fig. S5), indicating no hint of small-study effects and publication bias. The methodological quality was moderate in the included studies, and as three trials have only been reported in abstract form, their risk of bias couldn't be assessed accurately [13,23,24]. Generally, all the remaining studies were free of definite high risk of bias for random sequence generation, allocation concealment, incomplete outcome data, and selective reporting of outcomes (Supplementary Fig. S6).

4. Discussion

This updated network meta-analysis was based on 25 trials including 13,010 patients, and compared 23 first-line systemic treatments for mRCC. There are several principal findings. Firstly, pembrolizumab plus axitinib was probably the best option for OS, and statistically more effective than most available treatments (9/14). Secondly, though cabozantinib was the most preferred treatment strategy for prolonging PFS, it didn't provide significantly better OS benefit than sunitinib. Thirdly, temsirolimus and atezolizumab were the best tolerated. The ICI-based combination treatments (nivolumab plus ipilimumab, pembrolizumab plus axitinib, avelumab plus axitinib, and atezolizumab plus bevacizumab) resulted in fewer or similar high-grade AEs than sunitinib.

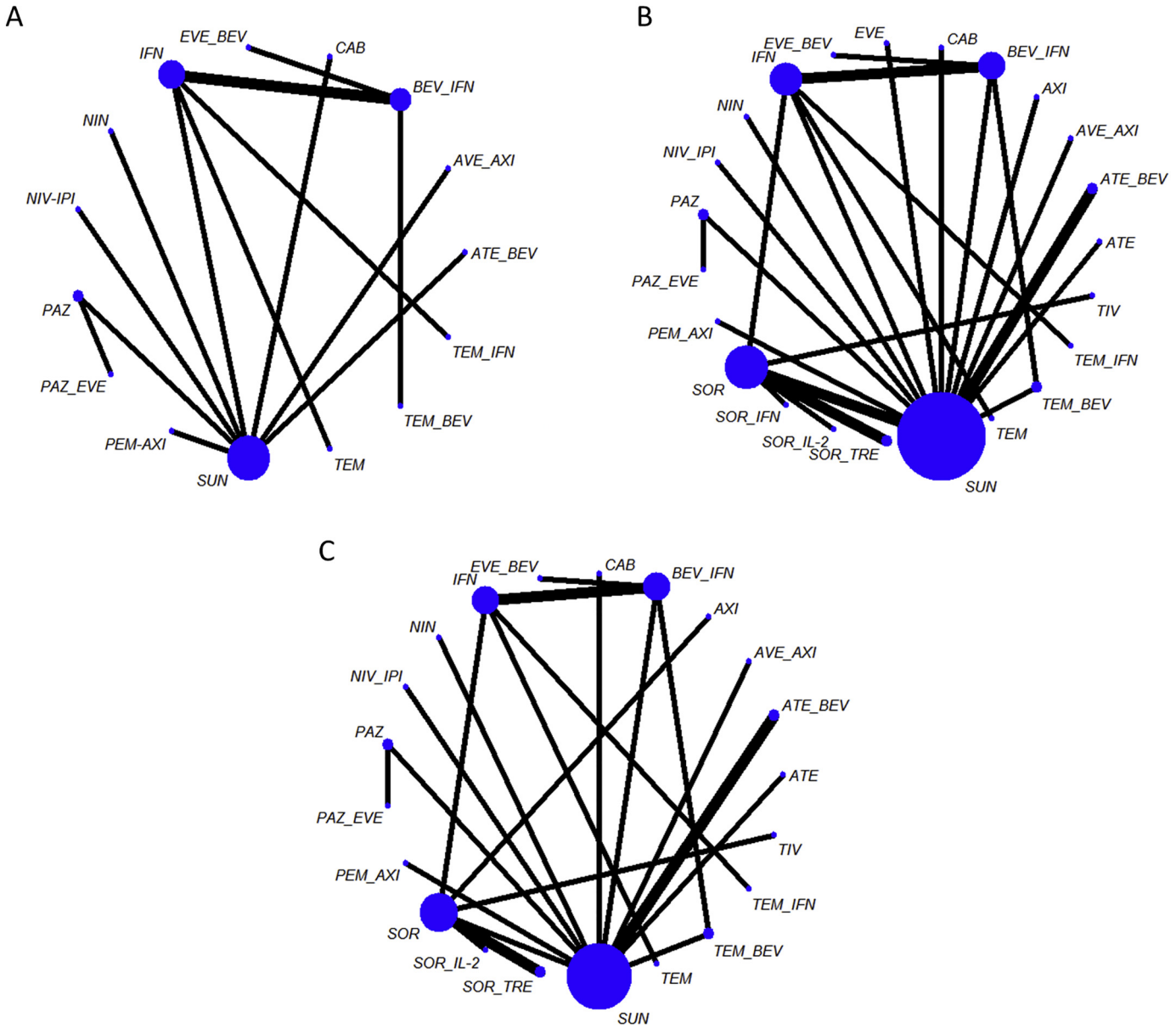

Fig. 2. Network of the comparisons for the Bayesian network meta-analysis. Network plot for (A) OS, (B) PFS and (C) high-grade AEs. The size of every treatment node corresponds to the number of randomly assigned patients. The width of the lines is proportional to the number of trials. SUN = sunitinib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib. AVE_AXI = avelumab plus axitinib. ATE_BEV = atezolizumab plus bevacizumab. EVE_BEV = everolimus plus bevacizumab. TEM_BEV = temsirolimus plus bevacizumab. TEM_IFN = temsirolimus plus interferon-α. PAZ_EVE = pazopanib plus everolimus. BEV_IFN = bevacizumab plus interferon-α. SOR_TRE = sorafenib plus trebananib. SOR_IL-2 = sorafenib plus interleukin-2. SOR_IFN = sorafenib plus interferon-α. PAZ = pazopanib. ATE = atezolizumab. TEM = temsirolimus. AXI = axitinib. TIV = tivozanib. NIN = nintedanib. EVE = everolimus. SOR = sorafenib. IFN = interferon-α.

In this meta-analysis, pembrolizumab plus axitinib appeared to be the best option based on OS. Obvious anti-tumor activity of axitinib or pembrolizumab used as monotherapy for patients with mRCC has been reported in previous studies [45,48]. Consequently, combination of pembrolizumab and axitinib was also tested, and results of a phase 1b trial showed that 73% of patients could have a response to this combination [49]. Data of pembrolizumab plus axitinib we used for analysis were derived from the KEYNOTE-426 trial. The results of KEYNOTE-426 trial was consistent with ours, showing that pembrolizumab plus axitinib resulted in significantly longer OS and PFS than sunitinib [11]. Moreover, survival benefit of pembrolizumab plus axitinib was observed across all risk groups, and independent of PD-L1 status [11].

Pembrolizumab plus axitinib is a combination of anti-PD-1 monoclonal antibody and VEGF receptor (VEGFR) TKI. Immune checkpoints, such as CTLA-4 and PD-1, are negative regulators that inhibit proliferation and activity of T cells, and blockade of immune checkpoints could result in tumor eradication by reactivating and enhancing internal T-cell response [50]. VEGF inhibition has been shown to suppress angiogenesis, and increase the recruitment and infiltration of T cells into the tumors [51–53]. Simultaneous blockade of PD-1 and VEGFR2 induced decreased tumor neovascularization, upregulation of pro-inflammatory cytokines, and tumor inhibition in a murine model [54]. These studies hinted that the combination of ICI and VEGF axis inhibitors could play an important role in the treatment of RCC, and subsequently a large number of trials were performed for testing the effectiveness of such combinations. Recently, besides pembrolizumab plus axitinib, avelumab (anti-PD-L1 antibody) plus axitinib, and atezolizumab (anti-PD-L1 antibody) plus bevacizumab (anti-VEGF monoclonal antibody) were respectively investigated in two large-scale RCTs (IMmotion 151 and JAVELIN Renal 101), and both of them showed significant advantages in survival for patients with mRCC compared with sunitinib [12,13].

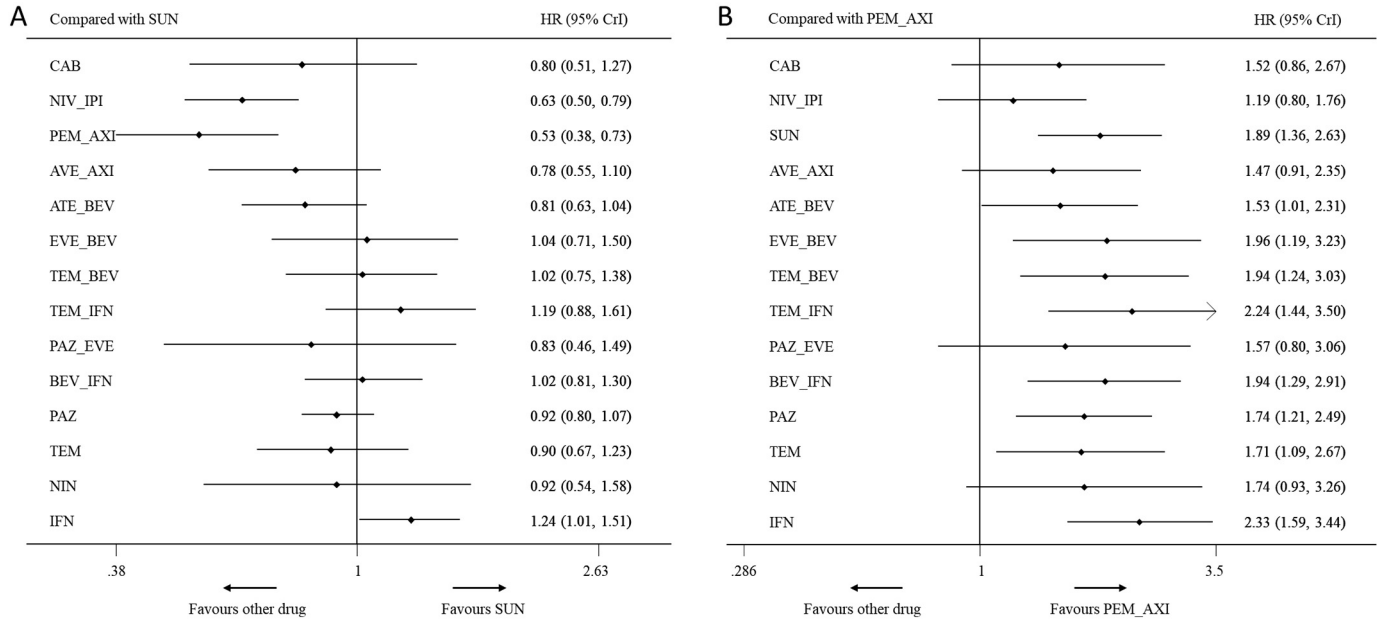

Fig. 3. Pooled hazard ratios for overall survival. (A) Forest plot, with sunitinib as the comparator; (B) Forest plot, with pembrolizumab plus axitinib as the comparator. HR = hazard ratio. CrI = credible interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib. AVE_AXI = avelumab plus axitinib. ATE_BEV = atezolizumab plus bevacizumab. EVE_BEV = everolimus plus bevacizumab. TEM_BEV = temsirolimus plus bevacizumab. TEM_IFN = temsirolimus plus interferon-α. PAZ_EVE = pazopanib plus everolimus. BEV_IFN = bevacizumab plus interferon-α. PAZ = pazopanib. TEM = temsirolimus. NIN = nintedanib. IFN = interferon-α.

However, head-to-head comparative trials regarding combinations of ICI and VEGF axis inhibitors (pembrolizumab plus axitinib, avelumab plus axitinib, and atezolizumab plus bevacizumab) are lacking. Our pooled analysis evaluating the effects of these three combinations revealed that pembrolizumab plus axitinib showed the best in the analysis of OS.

Of note, dual checkpoints inhibition with anti-PD-1 antibody nivolumab and anti-CTLA-4 antibody ipilimumab was explored for

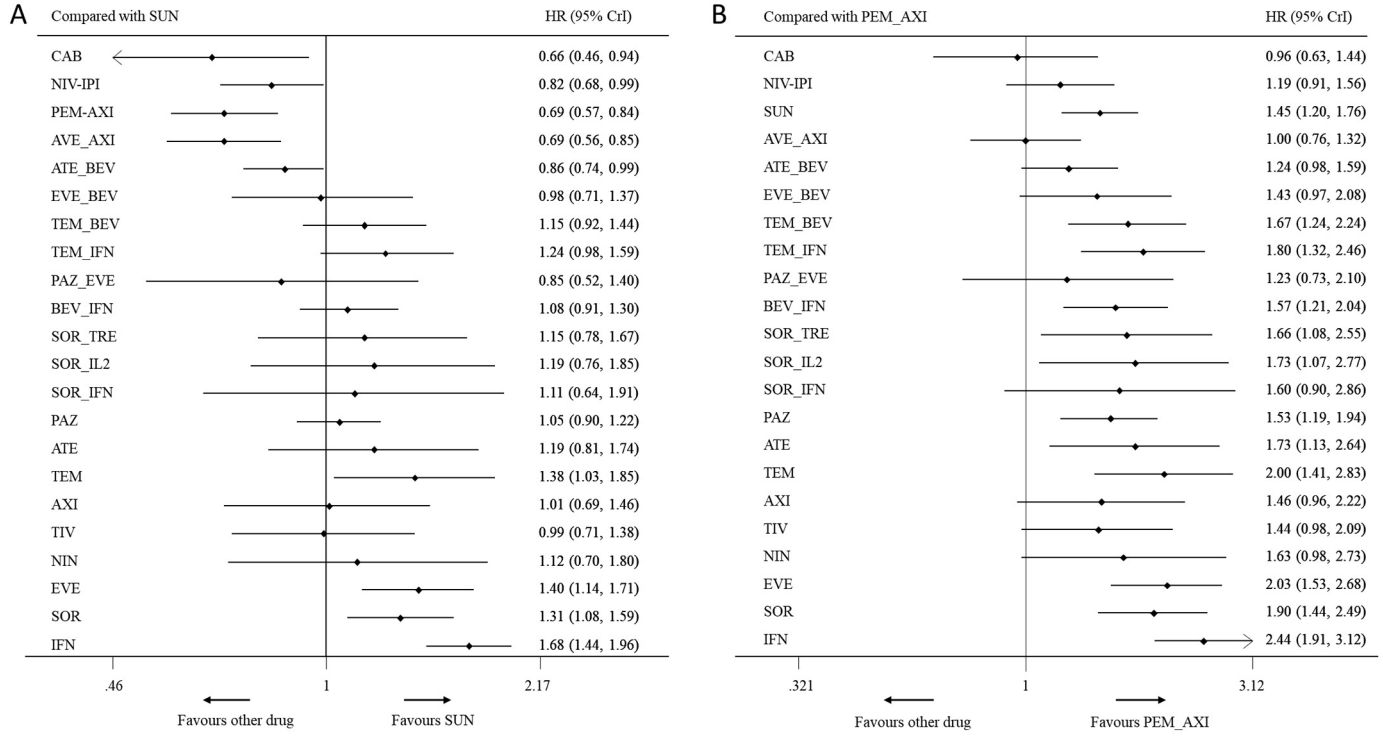

Fig. 4. Pooled hazard ratios for progression-free survival. (A) Forest plot, with sunitinib as the comparator; (B) Forest plot, with pembrolizumab plus axitinib as the comparator. HR = hazard ratio. CrI = credible interval. Numbers in parentheses indicate 95% credible intervals. SUN = sunitinib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib. AVE_AXI = avelumab plus axitinib. ATE_BEV = atezolizumab plus bevacizumab. EVE_BEV = everolimus plus bevacizumab. TEM_BEV = temsirolimus plus bevacizumab. TEM_IFN = temsirolimus plus interferon-α.PAZ_EVE = pazopanib plus everolimus. BEV_IFN = bevacizumab plus interferon-α. SOR_TRE = sorafenib plus trebananib. SOR_IL-2 = sorafenib plus interleukin-2. SOR_IFN = sorafenib plus interferon-α. PAZ = pazopanib. ATE = atezolizumab. TEM = temsirolimus. AXI = axitinib. TIV = tivozanib. NIN = nintedanib. EVE = everolimus. SOR = sorafenib. IFN = interferon-α.

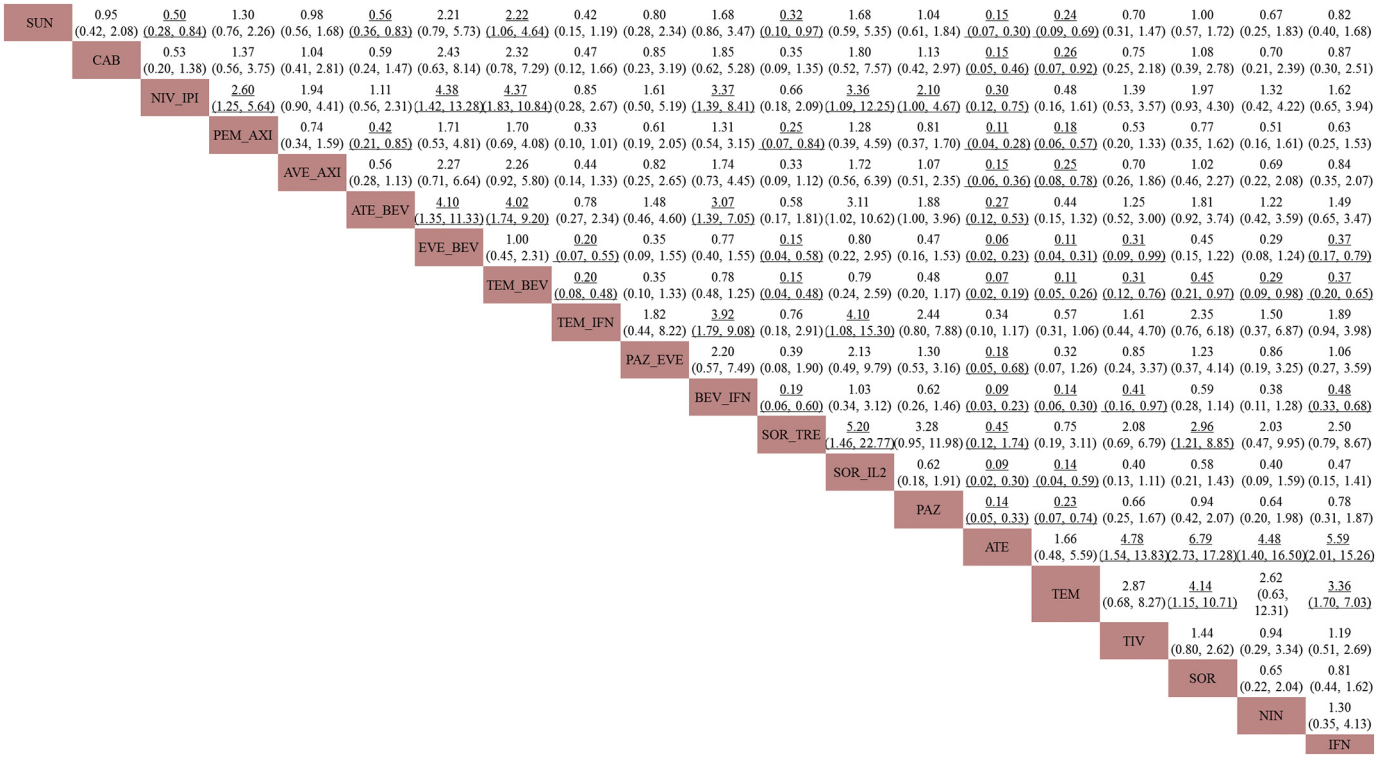

Fig. 5. Pooled odds ratios for high-grade adverse events. The column treatment is compared with the row treatment. ORs lower than 1 favor the column-defining treatment. Numbers in parentheses indicate 95% credible intervals. Significant results are underscored. SUN = sunitinib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib. AVE_AXI = avelumab plus axitinib. ATE_BEV = atezolizumab plus bevacizumab. EVE_BEV = everolimus plus bevacizumab. TEM_BEV = temsirolimus plus bevacizumab. TEM_IFN = temsirolimus plus interferon-α. PAZ_EVE = pazopanib plus everolimus. BEV_IFN = bevacizumab plus interferon-α. SOR_TRE = sorafenib plus trebananib. SOR_IL-2 = sorafenib plus interleukin-2. PAZ = pazopanib. ATE = atezolizumab. TEM = temsirolimus. TIV = tivozanib. SOR = sorafenib. NIN = nintedanib. IFN = interferon-α.

mRCC in CheckMate-214 trial, producing impressive results likewise [22]. In practice, however, nivolumab plus ipilimumab might not be as effective as pembrolizumab plus axitinib given concerns about results of ranking in our study. Though both pembrolizumab plus axitinib, and nivolumab plus ipilimumab were demonstrated significantly improved OS versus sunitinib, there was a 68% probability that pembrolizumab plus axitinib was the best choice for OS, whereas a 48% probability that nivolumab plus ipilimumab was the second. Moreover, pembrolizumab plus axitinib was also significantly more efficacious than monotherapies (pazopanib, temsirolimus, and IFN-α), and mTOR inhibitor- or cytokine-related combination therapies (atezolizumab plus bevacizumab, everolimus plus bevacizumab, temsirolimus plus bevacizumab, temsirolimus plus IFN-α, and bevacizumab plus IFN-α) as measured by OS in our study.

In terms of PFS, cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus axitinib, avelumab plus axitinib, and atezolizumab plus bevacizumab were statistically superior to sunitinib, and among these four treatments, cabozantinib was likely to be the preferred option followed by pembrolizumab plus axitinib, avelumab plus axitinib, and nivolumab plus ipilimumab. However, OS benefit for cabozantinib over sunitinib was not observed, while the ICI-based combination treatments including pembrolizumab plus axitinib, and nivolumab plus ipilimumab were significantly superior to sunitinib. The disparate efficacy of these treatments with respect to OS and PFS should be noticed. Hypothetically, this phenomenon could be explained by immunotherapy-induced pseudoprogression. Some patients treated with immunotherapies were observed to experience initial increased size of tumor, confirmed by biopsy as inflammatory cell infiltrates or necrosis [55,56]. This phenomenon was also observed in two phase 3 RCTs for metastatic breast cancer [57] and colorectal cancer [58], showing significant efficacy of the experimental treatments in terms of OS, but not of PFS. These previous studies together with our network meta-analysis demonstrated that the surrogacy of PFS for OS, the gold standard for registration trials, may be difficult to establish, and OS should remain the primary endpoint of clinical trials to assess efficacy of treatments, especially the ICI-based therapies.

We examined high-grade AEs as a measure of the toxicity of treatments. Though acceptability of temsirolimus and atezolizumab acceptability surpassed all the other treatments, their efficacy showing no significant survival benefits than sunitinib were unsatisfactory. Two combination treatments of mTOR inhibitor plus anti-VEGF antibody (everolimus plus bevacizumab, and temsirolimus plus bevacizumab) had the least favorable toxicity profile, while the ICI-based combination treatments were tolerated. Among the four ICI-based treatments, nivolumab plus ipilimumab, and atezolizumab plus bevacizumab were associated with significantly lower rate of high-grade AEs compared with sunitinib, and the safety profiles of pembrolizumab plus axitinib, and avelumab plus axitinib were similar to sunitinib. The observed toxicities of these combination therapies were on the basis of the known profiles of ICI and targeted agents. Different from targeted therapy, toxicities of ICI-based therapies, known as immune-related AEs (irAEs), are mostly attributable to a hyperactivated T-cell response resulting in reactivity against normal tissues [59], and commonly associated with fatigue, skin rash, colitis, and asymptomatic hepatitis [60]. Though patients received ICI-based therapies possibly experienced the irAEs, toxicity of ICI were mainly manageable. For example, although the incidence of high-grade elevations in liver-enzyme levels in the pembrolizumab-axitinib group was higher than previously observed when each agent was used as monotherapy, there were no deaths related to hepatic adverse events in the pembrolizumab-axitinib group [11]. However, we should noticed that discontinuation of treatment due to AEs occurred more frequently in the pembrolizumab-axitinib group than in the sunitinib group in KEYNOTE-426 trial [11]. Overall, our results indicated that ICI-based combination treatments had favorable balance between efficacy and acceptability, since they had better OS benefit, and not higher risk of toxicity versus sunitinib, and more

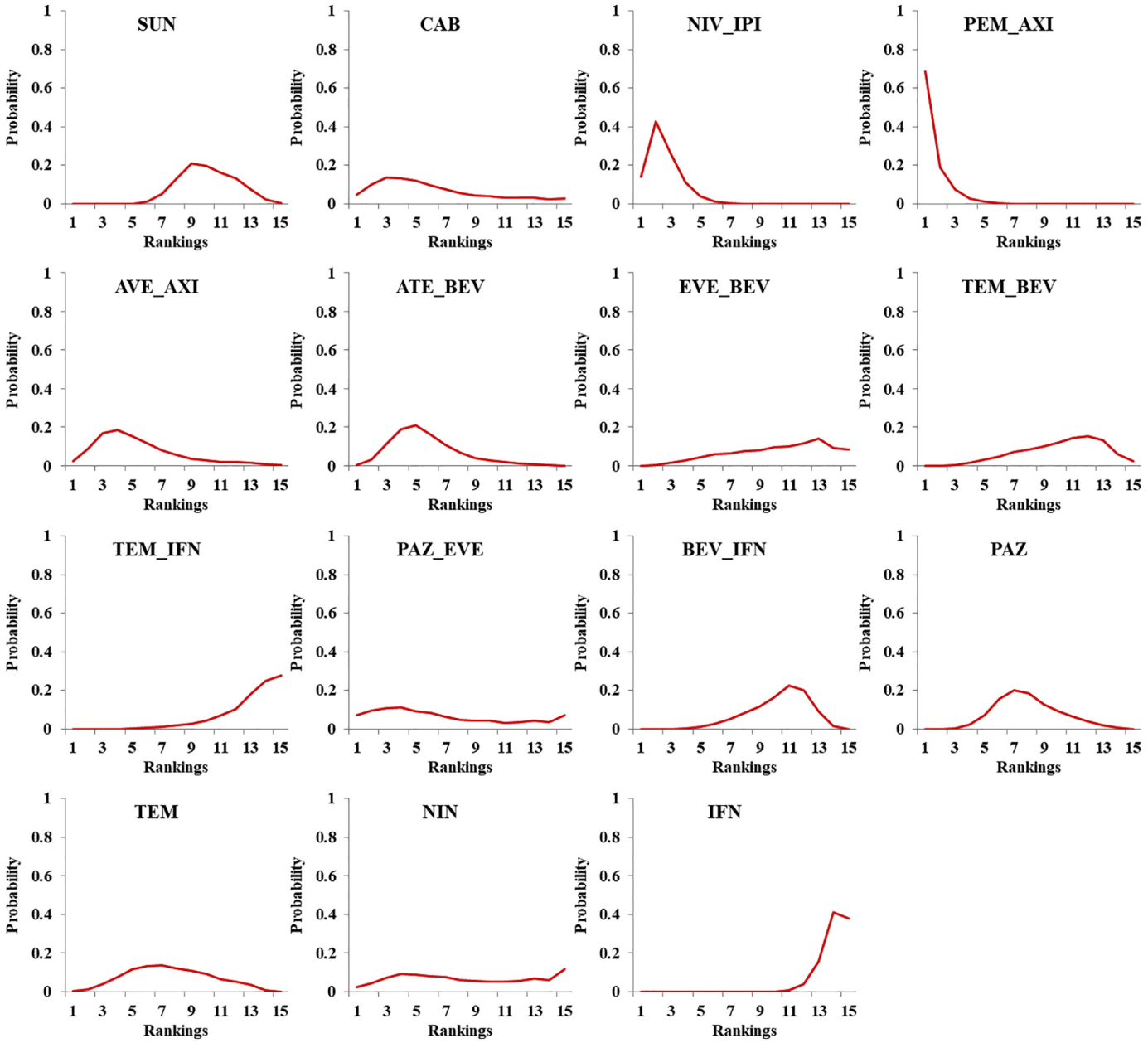

Fig. 6. Ranking of treatments in terms of overall survival. Rankograms were drawn according to distribution of the ranking probabilities. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on in terms of overall survival, among 15 treatments. SUN = sunitinib. CAB = cabozantinib. NIV_IPI = nivolumab plus ipilimumab. PEM_AXI = pembrolizumab plus axitinib. AVE_AXI = avelumab plus axitinib. ATE_BEV = atezolizumab plus bevacizumab. EVE_BEV = everolimus plus bevacizumab. TEM_BEV = temsirolimus plus bevacizumab. TEM_IFN = temsirolimus plus interferon-α. PAZ_EVE = pazopanib plus everolimus. BEV_IFN = bevacizumab plus interferon-α. PAZ = pazopanib. TEM = temsirolimus. NIN = nintedanib. IFN = interferon-α.

combination regimens with ICI-backbone were worth exploring in clinical trials.

Recently, a network meta-analysis by Wallis CJ et al evaluated first-line systemic therapies for mRCC, suggesting cabozantinib and nivolumab plus ipilimumab were likely to be the best first-line therapies [61]. Our meta-analysis differed from their study in several ways. First of all, our study included 25 available RCTs covering all the existing first-line systemic treatments for mRCC, whereas Wallis's study included only ten treatments. Among the RCTs we included, there were two large-scale, phase 3 RCTs (KEYNOTE-426 and JAVELIN Renal 101) published in 2019 comparing ICI related regimens (pembrolizumab plus axitinib, and avelumab plus axitinib) with sunitinib, and showing significant survival benefits for pembrolizumab plus axitinib, and avelumab plus axitinib versus sunitinib, respectively [11,12]. However, these two important RCTs were not involved in Wallis's study, which could explain the disparity between our results and their conclusions. In addition, we assessed OS as the primary outcome, while in Wallis's study, PFS was the primary outcome, and OS was the secondary outcome. Finally, we performed both fixed-effect and random-effect models for the assessment of OS, PFS, and high-grade AEs as well as standard pairwise comparisons between treatment arms to critically complement the results of the network meta-analysis, whereas the results of Wallis's study were only obtained from fixed-effect model.

The strengths of our study are as follows. First and foremost, to our knowledge, this study is the most comprehensive and systematic comparative meta-analysis of all available first-line systemic treatments for mRCC. Moreover, by using the Bayesian network meta-analysis, we were able to incorporates available information from RCTs, indirectly assess multiple treatments in the absence of head-to-head trials, and provide a rank order for treatments based on OS, PFS, and high-grade

AEs for mRCC [62,63]. Though multiple comparisons might lead to the inflation of type I error in theory, the type I error rate was demonstrated to be controlled in the Bayesian network meta-analysis [64].Also, various statistical models were used for analysis to ensure the reliability and accuracy of results. Finally, assessment of both efficacy and safety provides new insights into different systemic treatments, and may provide guidance to patients and clinicians, when making treatment decisions, and designing future comparative trials. However, limitations of our study should be taken into account. The principal limitation of this network meta-analysis was based on the reporting quality of trials reviewed, as might have been affected by several types of bias, such as from blinding of participants and outcome assessment, which may reduce the accuracy of overall findings. Since eligibility criteria were not identical cross trials, some characteristics of the patients might be different, which might limit the comparability of trials. Of note, caution should be warranted in assessing cabozantinib because data of cabozantinib could be only obtained from CABOSUN. Most of the other RCTs involved in our study enrolled patients in all risk strata, while CABOSUN only enrolled patients with intermediate- and poor-risk disease, thus there was a risk of unfairly estimating the efficacy of cabozantinib, when compared it with other systemic treatments. Based on nature of the study, CABOSUN is a randomized phase 2 trial with only 79 and 78 patients in each arms, and its results may be less authoritative compared with that of phase 3 RCTs. For example, in CABOSUN, PFS was assessed by the investigators without independent review and blindness, which resulted in a potential bias. Additionally, using PFS as the primary endpoint may also affect the assessment of the OS data of cabozantinib, since treatment was continued until disease progression, and therapies administered after progression, which were not prescribed in CABOSUN may lead to a consequent but not yet clear bias. Likewise, the results of CABOSUN were considered to be controversial based on a previous study [65]. Therefore, further phase 3 RCTs with OS as the primary endpoint are necessary for more accurately evaluating the efficacy of cabozantinib. Besides CABOSUN, due to the potential influence of the treatments administered after progression on OS, data from other trials with PFS as the primary endpoint should also be interpreted more cautiously. Moreover, in some of the trails with PFS as the primary endpoint, the OS benefits of the treatments were not evaluated, which made it impossible for us to assess the OS benefits of all the existing treatments comprehensively. Furthermore, this study was not an individual patient data-based meta-analysis. Though there were no major differences in study characteristics, some confounding factors (e.g., prognostic risk categories, PD-L1 status, etc.), which might influence the benefit of systemic treatments, but were not available at the individual patient level; thus analyses adjusted for these factors were impossible in our network meta-analysis. Finally, because some factors such as length of follow-up, number of organs with metastases and PD-L1 status were not reported in some of the trials, it was impossible for us to perform the meta-regression for these factors. Instead, we explored residual heterogeneity by sensitivity analyses (excluding studies with selection bias, with detection bias, that selected non-clear cell carcinoma subtype, and that were randomized phase 2 trials), and found that removing these studies did not substantially affect the results, indicating the robustness of the findings. Furthermore, it was supposed that meta-regression was appropriate for random-effect model [66], while our analysis was based on the fixed-effect model.

5. Conclusions

Our findings suggested that pembrolizumab plus axitinib provided the best OS benefit for metastatic RCC. Cabozantinib is the most preferred option for PFS, but it is less effective than pembrolizumab plus axitinib and nivolumab plus ipilimumab for OS. Nivolumab plus ipilimumab might also be a potent choice for metastatic RCC since it had the most favorable balance between efficacy and acceptability. Considering the limitation of this analysis, further head-to-head comparative RCTs are required to confirm our results.

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Author contributions

Junpeng Wang, Xin Li and Tianzhong Yan conceived and designed the study. Junpeng Wang, Xin Li, Xiaoqiang Wu and Zhiwei Wang collected data and performed systemic review. Junpeng Wang, Xin Li, Chan Zhang, Guanghui Cao, Xiaofan Zhang and Feng Peng performed the meta-analysis. Junpeng Wang, Xin Li and Tianzhong drafted, edited and revised the manuscript. Junpeng Wang and Xin Li contributed equally to this work.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2019.08.006.

References

[1] Stitzlein L, Rao P, Dudley R. Emerging oral VEGF inhibitors for the treatment of renal cell carcinoma. Expert Opin Investig Drugs 2019;28(2):121–30.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68(1):7–30.
[3] Posadas EM, Limvorasak S, Figlin RA. Targeted therapies for renal cell carcinoma. Nat Rev Nephrol 2017;13(8):496–511.
[4] Considine B, Hurwitz ME. Current status and future directions of immunotherapy in renal cell carcinoma. Curr Oncol Rep 2019;21(4):34.
[5] Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol 1995;13(3):688–96.
[6] McDermott DF, Regan MM, Clark JI, Flaherty LE, Weiss GR, Logan TF, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol 2005;23(1):133–41.
[7] Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov 2018;8(9):1069–86.
[8] Cella D, Grunwald V, Escudier B, Hammers HJ, George S, Nathan P, et al. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. Lancet Oncol 2019;20(2):297–310.
[9] Jonasch E. NCCN Guidelines Updates: Management of Metastatic Kidney Cancer. J Natl Compr Cancer Netw 2018;17(5.5):587–9.
[10] Powles T, Albiges L, Staehler M, Bensalah K, Dabestani S, Giles RH, et al. Updated European association of urology guidelines recommendations for the treatment of first-line metastatic clear cell renal cancer. Eur Urol 2017;73(3):311–5.
[11] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380(12):1116–27.
[12] Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380(12):1103–15.
[13] Motzer RJ, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, et al. IMmotion151: a randomized phase III study of atezolizumab plus bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC). J Clin Oncol 2018;36:578.
[14] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162(11):777–84.
[15] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011;343:d5928.
[16] Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: A generalised linear modelling framework for pairwise and network meta-analysis

of randomised controlled trials. NICE Decision Support Unit Technical Support Documents. London; 2014.
[17] van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res Synth Methods 2012;3(4):285–99.
[18] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
[19] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64(2):163–71.
[20] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[21] Spiegelhalter DJ, Best NG, Carlin BR, van der Linde A. Bayesian measures of model complexity and fit. J Roy Stat Soc B 2002;64:583–616.
[22] Gelman A, Rubin DB. Markov chain Monte Carlo methods in biostatistics. Stat Methods Med Res 1996;5(4):339–55.
[23] Simillis C, Li T, Vaughan J, Becker LA, Davidson BR, Gurusamy KS. Methods to decrease blood loss during liver resection: a network meta-analysis. Cochrane Database Syst Rev 2014;4:CD010683.
[24] Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012;3(2):80–97.
[25] Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8(10):e76654.
[26] Motzer RJ, Tannir NM, McDermott DF, Aren FO, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378(14):1277–90.
[27] Tomita Y, Naito S, Sassa N, Takahashi A, Kondo T, Koie T, et al. Sunitinib versus sorafenib as first-line therapy followed by sorefenib and sunitinib for patients with metastatic renal cell carcinoma (RCC) with clear cell histology: A multicenter randomized trial, CROSS-J-RCC. J Clin Oncol 2017;35:469.
[28] McDermott DF, Atkins MB, Motzer RJ, Rini B, Escudier BJ, Fong L, et al. A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts). J Clin Oncol 2017;35:431.
[29] Cirkel GA, Hamberg P, Sleijfer S, Loosveld OJL, Dercksen MW, Los M, et al. Alternating treatment with pazopanib and everolimus vs continuous pazopanib to delay disease progression in patients with metastatic clear cell renal cell cancer. JAMA Oncol 2017;3(4):501.
[30] Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. J Clin Oncol 2017;35(6):591–7.
[31] Ravaud A, Barrios CH, Alekseev B, Tay MH, Agarwala SS, Yalcin S, et al. RECORD-2: phase II randomized study of everolimus and bevacizumab versus interferon α-2a and bevacizumab as first-line therapy in patients with metastatic renal cell carcinoma. Ann Oncol 2015;26(7):1378–84.
[32] Eisen T, Loembé A-B, Shparyk Y, MacLeod N, Jones RJ, Mazurkiewicz M, et al. A randomised, phase II study of nintedanib or sunitinib in previously untreated patients with advanced renal cell cancer: 3-year results. Br J Cancer 2015;113(8):1140–7.
[33] Eichelberg C, Vervenne WL, De Santis M, Fischer Von Weikersthal L, Goebell PJ, Lerchenmüller C, et al. SWITCH: a randomised, sequential, open-label study to evaluate the efficacy and safety of Sorafenib-sunitinib versus Sunitinib-sorafenib in the treatment of metastatic renal cell cancer. Eur Urol 2015;68(5):837–47.
[34] Rini BI, Bellmunt J, Clancy J, Wang K, Niethammer AG, Hariharan S, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. J Clin Oncol 2014;32(8):752–9.
[35] Motzer RJ, Barrios CH, Kim TM, Falcon S, Cosgriff T, Harker WG, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32(25):2765–72.
[36] Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: the ROSORC trial. Br J Cancer 2011;104(8):1256–61.
[37] Négrier S, Gravis G, Pérol D, Chevreau C, Delva R, Bay J-O, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol 2011;12(7):673–80.
[38] Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369(8):722–31.
[39] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27(22):3584–90.
[40] Jonasch E, Corn P, Pagliaro LC, Warneke CL, Johnson MM, Tamboli P, et al. Upfront, randomized, phase 2 trial of sorafenib versus sorafenib and low-dose interferon alfa in patients with advanced renal cell carcinoma. Cancer 2010;116(1):57–65.
[41] Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou S-S, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008;26(33):5422–8.
[42] Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356(22):2271–81.
[43] Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370(9605):2103–11.
[44] Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013;31(30):3791–9.
[45] Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncol 2013;14(13):1287–94.
[46] Rini B, Szczylik C, Tannir NM, Koralewski P, Tomczak P, Deptala A, et al. AMG 386 in combination with sorafenib in patients with metastatic clear cell carcinoma of the kidney. Cancer 2012;118(24):6152–61.
[47] Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27(8):1280–9.
[48] McDermott DF, Lee JL, Szczylik C, Donskov F, Malik J, Alekseev BY. Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (accRCC): Results from cohort A of KEYNOTE-427. J Clin Oncol 2018;36(15).
[49] Atkins MB, Plimack ER, Puzanov I, Fishman MN, McDermott DF, Cho DC, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncol 2018;19(3):405–15.
[50] Carlo MI, Voss MH, Motzer RJ. Checkpoint inhibitors and other novel immunotherapies for advanced renal cell carcinoma. Nat Rev Urol 2016;13(7):420–31.
[51] Shrimali RK, Yu ZY, Theoret MR, Chinnasamy D, Restifo NP, Rosenberg SA. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010;70(15):6171–80.
[52] Manning EA, Ullman JGM, Leatherman JM, Asquith JM, Hansen TR, Armstrong TD, et al. A vascular endothelial growth factor receptor-2 inhibitor enhances antitumor immunity through an immune-based mechanism. Clin Cancer Res 2007;13(13):3951–9.
[53] Huang YH, Yuan JP, Righi E, Kamoun WS, Ancukiewicz M, Nezivar J, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. P Natl Acad Sci USA 2012;109(43):17561–6.
[54] Yasuda S, Sho M, Yamato I, Yoshiji H, Wakatsuki K, Nishiwada S, et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo. Clin Exp Immunol 2013;172(3):500–6.
[55] George S, Motzer RJ, Hammers HJ, Redman BG, Kuzel T, Tykodi SS, et al. Safety and efficacy of nivolumab in patients with metastatic renal cell carcinoma treated beyond progression a subgroup analysis of a randomized clinical trial. JAMA Oncol 2016;2(9):1179–86.
[56] Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. J Clin Oncol 2015;33(31):3541.
[57] Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377(9769):914–23.
[58] Stintzing S, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. Lancet Oncol 2016;17(10):1426–34.
[59] Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33(17):1974–82.
[60] Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. J Clin Oncol 2015;33(18):2092–9.
[61] Wallis CJD, Klaassen Z, Bhindi B, Ye XY, Chandrasekar T, Farrell AM, et al. First-line systemic therapy for metastatic renal cell carcinoma: a systematic review and network meta-analysis. Eur Urol 2018;74(3):309–21.
[62] Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. Bmj 2005;331(7521):897–900.
[63] Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23(20):3105–24.
[64] Uhlmann L, Jensen K, Kieser M. Hypothesis testing in Bayesian network meta-analysis. BMC Med Res Methodol 2018;18(1):128.
[65] Buti S, Bersanelli M. Is cabozantinib really better than sunitinib as first-line treatment of metastatic renal cell carcinoma? J Clin Oncol 2017;35(16):1858–9.
[66] Borenstein M. Introduction to Meta-analysis. Chichester, U.K.: John Wiley & Sons; 2009; xxviii (421 pp.).