A network meta-analysis of efficacy and safety of first-line and second-line therapies for the management of metastatic renal cell carcinoma

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Abstract

What is known and objective: Metastatic renal cell carcinoma (mRCC) is the most common type of kidney cancers. Disease-specific survival for mRCC has been significantly improved with the introduction of new targeted agents since 2005. However, there is a lack of head-to-head clinical trials comparing the efficacy between therapies. This study compared indirectly progression-free survival (PFS) and overall survival (OS) among first-line and second-line therapies in patients with mRCC using network meta-analysis (NMA).

Methods: The PubMed, MEDLINE, Cochrane Library and Web of Science were searched to identify phase II or phase III randomized controlled trials (RCTs) of targeted and biological therapies in patients with mRCC published between January 2000 and June 2020. The Bayesian fixed-effect NMA was performed to evaluate relative PFS and OS of first-line and second-line therapies of axitinib, bevacizumab, cabozantinib, everolimus, lenvatinib, nivolumab, ipilimumab, pazopanib, sorafenib, sunitinib, temsirolimus, tivozanib, avelumab and pembrolizumab, which were approved by the Food and Drug Administration or European Medicines Agency. End points were compared using hazard ratio (HR) and 95% credible interval (CrI). The surface under the cumulative ranking curve (SUCRA) was estimated to assess the probability of being the best treatment.

Results and discussion: A total of 26 RCTs (first line: 19, second line: 9) with 13 893 patients were included in the NMA. For the first-line therapy, cabozantinib was associated with the highest improved PFS (HR = 0.26, 95% CrI = 0.14-0.44) followed by avelumab + axitinib and pembrolizumab + axitinib (HR = 0.27, SUCRA = 90%). Pembrolizumab + axitinib had a high likelihood of being the preferred treatment when using OS as the outcome measure (HR = 0.41, 95% CrI = 0.16-0.85). Avelumab + axitinib had the lowest HR compared with placebo + interferon on discontinuations due to AE (HR = 1.04, 95% CrI = 0.54-1.86). For second-line therapy, cabozantinib was identified as the most effective treatment option when assessing PFS (HR = 0.17, 95% CrI = 0.12-0.24). Axitinib had the lowest HR of OS and discontinuation due to
1 | WHAT IS KNOWN AND OBJECTIVE

In the United States, kidney cancer is the eighth and tenth most prevalent form of cancer in men and women, respectively. An estimated 73,820 incident cases and 14,770 deaths from kidney cancer were reported in 2019. Renal cell carcinoma (RCC) is the most common type of kidney cancer and accounts for approximately 90% of the diagnosed kidney cancer cases. There are several types of RCC, including clear cell RCC, papillary RCC, chromophobe RCC, collecting duct carcinoma and other rare types of RCC. Of the different types of RCC, clear cell RCC is the most common accounting for a prevalence of approximately 70%.2,3

The major treatment options for RCC include surgery, radiation therapy, immunotherapy, targeted therapy and chemotherapy. Approximately 70%-80% of patients with RCC have localized disease at the time of diagnosis, and surgery (eg nephrectomy) is an effective intervention and a potential cure for those with early-stage RCC. However, nephrectomy alone is not sufficient for patients experiencing recurrence after nephrectomy or having metastatic disease at the time of diagnosis, and few options were available for those patients before 2005. Traditional treatments, including radiation therapy, chemotherapy, and hormone therapy, are less used in patient with metastatic RCC (mRCC), whereas the most commonly used treatments have been targeted therapies or immunotherapy. Prior to 2005, immunotherapy was a dominant treatment option in patients with mRCC. Starting in the late 1980s, cytokines were considered the main treatment options for mRCC. The cytokines used most often to treat mRCC were interleukin-2 (IL-2) and interferon α (IFN-α). Since 2005, the use of cytokines have gradually declined due to the advent of the newer targeted treatment agents for the treatment of mRCC, which significantly improved disease-specific survival for mRCC.

By June 2020, the following targeted agents have been approved for the treatment of mRCC by the Food and Drug Administration (FDA): sorafenib (Nexavar®), sunitinib (Sutent®), temsirolimus (Torisel®), everolimus (Afinitor®), bevacizumab (Avastin®), pazopanib (Votrient®), axitinib (Inlyta®), cabozantinib (Cabometyx® ) and lenvatinib (Lenvima®). Tivozanib (Fotivda®) has been approved by the European Medicines Agency (EMA). These agents can be classified into following groups by their mechanism: small-molecule multiple tyrosine kinases inhibitor (TKI) including sorafenib, sunitinib, pazopanib, axitinib, cabozantinib and lenvatinib work by directly inhibiting multiple receptors such as the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) or Fms-like tyrosine kinase receptor-3 and thus blocking angiogenesis, and tivozanib is the VEGFR TKI, which inhibits VEGF; temsirolimus and everolimus work by inhibiting mammalian target of rapamycin (mTOR); and bevacizumab works as monoclonal antibodies that bind directly with vascular endothelial growth factor (VEGF) and prevent the engagement with its receptor. In addition, the FDA has approved a biologic agent, nivolumab (Opdivo®), which is a PD-1 (programmed cell death 1) immune checkpoint inhibitor, for the treatment of mRCC in 2015. Ipilimumab (Yervoy®), which is a monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4, was approved as the combination therapy with nivolumab in April 2018. Additional PD-1 immune checkpoint inhibitor such as pembrolizumab (Keytruda®) and avelumab (Bavencio®) were approved with axitinib in combination therapies in 2019. Appendix S1 summarizes the targeted and biologic agents approved for the treatment of mRCC.

Several randomized controlled trials (RCTs) have demonstrated the efficacy and safety of each of these targeted therapies in patients with mRCC, but head-to-head comparisons are lacking. Previous indirect network meta-analysis (NMA) studies have compared the efficacy and safety of some targeted therapies for the treatment of mRCC to address this gap in RCTs. However, there are no prospective clinical trials directly comparing the efficacy and safety

What is new and conclusion: With respect to PFS and OS improvement, cabozantinib, avelumab + axitinib and pembrolizumab + axitinib are likely to be the preferred options for the first-line therapy and cabozantinib and axitinib for the second-line therapy in the management of mRCC. Regarding safety, avelumab + axitinib and temsirolimus were considered preferred treatment options in first-line and second-line therapies. More future research is needed to establish subgroup analyses, allowing evaluation of the impact of some of the differences in patient characteristics, including treatment effect modifiers.

KEYWORDS
network meta-analysis, overall survival, progression-free survival, renal cell carcinoma, safety, targeted therapy

AE (HR = 0.54, 95% CI = 0.40-0.71; HR = 0.98, 95% CI = 0.42-1.97, respectively). Pazopanib was the second choice in terms of OS (HR = 0.56, 95% CI = 0.28-1.00; SUCRA = 76%) compared with placebo.
of all possible options of targeted and biologic agents by including nivolumab, cabozantinib, ipilimumab, pembrolizumab and avelumab.

Furthermore, there is no evidence in the literature regarding the efficacy and safety in both the first-line treatment and the second-line treatment for mRCC within a study. Therefore, the primary objective of this study was to compare overall survival (OS) and progression-free survival (PFS) of targeted and biologic agents approved by the FDA or EMA assessing both the first-line and the second-line treatments for mRCC. In addition, a secondary objective was to compare discontinuation rates due to toxicity in patients with mRCC.

2 | METHODS

2.1 | Search strategy

Databases including PubMed, MEDLINE, Cochrane Library and Web of Science were searched to identify phase II and/or phase III RCTs of targeted and biological therapies approved by the FDA or EMA to treat mRCC published between January 2000 and June 2020, when the search was completed. The search strategy consisted of key terms related to the interventions of interest and the terms used to describe renal cancer including renal cancer carcinoma, mRCC, advanced RCC, renal tumour, renal neoplasm and kidney cancer. Additional publications not captured in the electronic database search were sought through a grey literature search using Clinicaltrials.gov and Google Scholar.

2.2 | Study selection and evaluation

The study selection process was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Two independent reviewers (JH and CP) performed a first-stage screening of the titles and the abstracts identified in the initial search against the inclusion and exclusion criteria. Based on this initial screening, selected full-text articles were obtained and reviewed in the second stage of screening.

Studies that met the following inclusion criteria and clear description of the patients’ characteristics were included in the NMA:

1. Population of interest: Patients with mRCC.
2. Interventions: Targeted or biologic agents (or combination therapy) approved by the US FDA or the European Medicines Agency (EMA) and used in the first-line or second-line therapy (ie axitinib, bevacizumab, cabozantinib, everolimus, lenvatinib, nivolumab, ipilimumab, pazopanib, sorafenib, sunitinib, temsirolimus, tivozanib, pembrolizumab, avelumab, IFN and IL.
3. Comparators: Placebo or one of the regimes described under interventions used as first-line or second-line therapy.
4. Outcomes: PFS, OS (in the form of hazard ratio [HR]) or discontinuation rate due to toxicity (the number of patients who discontinued the trials due to adverse events).
5. Study Design: Phase II or III RCTs.

Articles were excluded according to the following criteria:

1. Published prior to 2000.
2. Interventions not of interest (eg not approved for mRCC).
3. Indications not of interest.
4. Outcomes not of interest (eg no clinical event outcomes of interest).
5. Non-RCT (eg cohort, case-control, cross-sectional studies, systematic literature reviews, commentaries and other meta-analyses).
6. Animal study.
7. Paediatric patients only (<18 years old).
8. Phase I.
9. Non-English articles.

Articles passing the two-stage screening process proceeded to the extraction stage where three reviewers (JH, CP and SG) independently performed data extraction. The following data elements of study design and demographic and clinical characteristics of the participants in each treatment arm were extracted: RCT name, year, sample size, age, gender, duration of follow-up, Eastern Cooperation Oncology Group score, Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk score, the number of metastatic sites, previous nephrectomy use, radio therapy, and the primary and secondary end points of the study.

In order to assess whether it was feasible to perform a valid NMA to compare interventions of interest, a feasibility assessment was conducted before performing the NMA. The NMA feasibility algorithm was adopted from Cope et al (2014). The first step included network identification to ensure treatments of interest are connected. Second, an assessment of similarity/transitivity was performed to identify differences in treatment definitions, outcome characteristics, and study and patient characteristics. Third, a heterogeneity of observed treatment effects was assessed using the consistency test. The consistency for closed loop was tested if there was a discrepancy between direct and indirect comparisons.

The risk of bias in each included trial was assessed using the Cochrane risk-of-bias assessment tool to determine the quality of studies by two independent reviewers (SP and JH). Seven specific domains were assessed: selection bias including random sequence generation and allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective outcome reporting and other sources of bias. Each study was assigned a ‘low’, ‘high’ or ‘unclear/unknown’ risk of bias for each item.

2.3 | Statistical analysis

Network meta-analysis is a methodology for synthesizing evidence to inform relative treatment effects from indirect and direct comparisons. In contrast to conventional meta-analyses, NMA allows simultaneous comparisons and pooling of multiple treatments.
study utilized the generalized linear modelling framework using a Bayesian Markov Chain Monte Carlo (MCMC) approach to conduct the NMA. Results of the NMA represented the posterior distributions of the model parameters, including point estimates of HR and 95% credible intervals (CrI), indicating the range of true underlying effects with 95% probability. In addition, the surface under the cumulative ranking curve (SUCRA), and rank probability for all treatments, and the probability that one treatment is better than a specific comparator were also calculated. SUCRA is a proportion, interpreted as the probability that the intervention in an outcome would be ranked first, which equals 100% when the treatment is certain to be the best and 0% when it would be the worst.

Model specification recommended by NICE was employed for each end point. For the PFS and OS, because the different follow-up time by trials may cause bias when estimates were calculated, HR and its SE was used instead of PFS or OS time. We assumed a normal distribution for the continuous relative measure (ie HR) of treatment effect of arm k relative to arm 1 in trial i, \( y_{ik} \), with variance \( V_{ik} \),

\[
y_{ik} \sim N(\theta_{ik}, V_{ik}).
\]

The case where the \( y_{ik} \) are log-hazard ratios was applied, with variance based on the normal theory approximation.

For the safety end points of the discontinuation due to AE, HR was generated adjusting for follow-up times. The different length of follow-up time in each trial was adjusted by the underlying assumption of the Poisson process for each trial arm, with a constant event rate \( \delta_{ik} \). This indicated that hazards are constant in each trial within follow-up time. The linear modelling followed Equation 2.

\[
\theta_{ik} = \text{cloglog}(p_{ik}) = \log \left( f_{ik} \right) + \mu_i + \delta_{ik},
\]

where \( r_{ik} \) is the number of events in arm k of trial i, with follow-up time \( f_{ik} \), the treatment effects \( \delta_{ik} \) is the log-hazard ratios form of study-specific treatment effects, \( \theta_{ik} \) is linear predictor of complementary log-log (cloglog) form of probability of events, and \( \mu_i \) is trial-specific baselines. This model allowed to generate the probability of a discontinuation due to AE within follow-up time. The pooled relative estimates were presented as HR for each pairwise comparisons.

The sampling was performed using OpenBUGS version 3.2.3 (Free Software Foundation, Inc., Boston, MA, USA), which is a stand-alone software application for the Bayesian analysis using the MCMC method. Non-informative prior distributions were used. Point estimates of the HR for each pair of treatments and 95% CrIs were calculated from 200 000 simulated draws from the posterior distribution after a burn-in of 100 000 iterations with three chains. The code for OpenBUGS is shown in Appendix S2. StataIC 14 (StataCorp LLC, College Station, TX, USA) was used to create network plots for each endpoint and meta-analysis for treatment effects in a pairwise comparison (metan command) to assess the heterogeneity of treatment effects. To check the assumption of consistency, the ifplot command was used to identify all closed loops in the network to estimate the respective inconsistency factors and their uncertainties. This provided the inconsistency plot, presenting the estimated inconsistency factor that is truncated at 0.27.

3 | RESULTS

3.1 | Study selection and network

A total of 26 RCTs (first line: 19; second line: 9) with 13 893 patients were included in the NMA (Figure 1). The study design and population characteristics are described in Table 1. Most trials were comprised of 70% males with an age of 60 years on average and were followed for 1 to 5 years. The trials included 23 interventions including combination therapies: axitinib, bevacizumab + IFN, cabozantinib, everolimus, IFN, lenvatinib, lenvatinib + everolimus, nivolumab, nivolumab + ipilimumab, pazopanib, pazopanib + everolimus, placebo, placebo + IFN, sorafenib, sorafenib + IFN, sorafenib + IL-2, sunitinib, temsirolimus, temsirolimus + bevacizumab, temsirolimus + IFN, tivozanib, avelumab + axitinib and pembrolizumab + axitinib. All interventions formed a connected network including direct and indirect comparisons for each end point (Figure 2).

The results of risk of bias assessment by first-line and second-line therapies are presented in Appendices S3 and S4, respectively. The complete network of the trials showed that all pairwise comparisons had only one trial (Table 1). In the first-line therapy, the most commonly used standard treatment arm was sunitinib (eight trials: CheckMate 214, RECORD-3, CABOSUN, COMPAX, SWITCH, SUTENT, JAVELIN Renal 101 and Keynote-426) followed by sorafenib (five trials: Escudier (2009), Hutson (2013), SWITCH, Jonasch (2010) and AV-951-09-301). Sorafenib (four trials: AXIS, TARGET, SWITCH and INTORSECT) and everolimus (four trials: Motzer (2015a), Motzer (2015b), METEOR and RECORD-1) were the most common therapies used in the second-line therapy.

In the feasibility assessment, analysis of inconsistency between direct and indirect comparisons of sunitinib, everolimus and IFN-a indicated that no statistically significant inconsistency was identified in the network for the discontinuation due to adverse events on the first-line therapy (the ratio of odds ratios (ROR) = 1.48, 95% CI = 1.00-3.55, Appendix S5).

3.2 | First-line therapy

For the first-line therapy, most interventions were statistically superior to placebo in increasing PFS of patients with mRCC. Cabozantinib was significantly associated with improved PFS (HR = 0.26, 95% CrI = 0.14-0.44) compared with placebo (Figure 3A). Cabozantinib had 91% of SUCRA and the probability of being first rank was 0.42, which was the highest among all treatments available followed by avelumab + axitinib and pembrolizumab + axitinib (HR = 0.27, SUCRA = 90%) (Table 2). For OS, pembrolizumab + axitinib had a high likelihood of being the preferred treatment for OS.
Nivolumab + ipilimumab was ranked as the second treatment regarding HR (0.48, 95% CrI = 0.19-1.03) and SUCRA (89%). For the discontinuation rates due to AE, axitinib + nivolumab had the lowest HR compared with placebo + IFN (HR = 1.04, 95% CrI = 0.54-1.86; Figure 3C). Most combination therapies had a higher risk of discontinuation due to AE (ie bevacizumab + IFN, temsirolimus + bevacizumab, pazopanib + everolimus, nivolumab + ipilimumab and pembrolizumab + axitinib) compared with monotherapies. The intervention with the highest HR on safety was pembrolizumab + axitinib (HR = 4.59, 95% CrI = 2.30-8.48; SUCRA = 5%).

**FIGURE 1** PRISMA flow diagram of the study selection process for NMA. NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
TABLE 1 Characteristics of the included trials

| Trial            | Year | Therapy line | Intervention (n) | Follow-up time, y | Median age, y | No. of males, (%) |
|------------------|------|--------------|------------------|-------------------|---------------|-------------------|
| CheckMate 214    | 2019 | 1st line     | Nivolumab + Ipilimumab (425) | 3.8              | 62            | 314 (74)          |
|                  |      |              | Sunitinib (422)   |                   |               |                   |
| CABOSUN          | 2017 | 1st line     | Cabozantinib (79) | 3.2              | 61            | 301 (71)          |
|                  |      |              | Sunitinib (78)    |                   |               |                   |
| Hutson (2017)    | 2017 | 1st line     | Axitinib (192)    | 4.5              | 58            | 134 (70)          |
|                  |      |              | Sorafenib (96)    | 4.5              | 58            | 74 (77)           |
| ROPETAR          | 2017 | 1st line     | Pazopanib + Everolimus (52) | 2.0              | 65            | 38 (73)           |
|                  |      |              | Pazopanib (49)    |                   |               |                   |
| INTORACT         | 2014 | 1st line     | Temsirolimus + Bevacizumab (400) | 3.3              | 59            | 286 (72)          |
|                  |      |              | Bevacizumab + IFN (391) | 3.3              | 38            | 270 (69)          |
| RECORD-3         | 2014 | 1st line     | Everolimus (238)  | 2.8              | 62            | 166 (70)          |
|                  |      |              | Sunitinib (233)   | 2.8              | 62            | 176 (76)          |
| AV-951-09-301    | 2013 | 1st line     | Tivozanib (260)   | 2.7              | 59            | 185 (71)          |
|                  |      |              | Sorafenib (257)   | 2.7              | 59            | 189 (74)          |
| COMPARZ          | 2013 | 1st line     | Pazopanib (557)   | 3.3              | 61            | 398 (71)          |
|                  |      |              | Sunitinib (553)   | 3.3              | 62            | 415 (75)          |
| ROSORC           | 2013 | 1st line     | Sorafenib + IL-2 (66) | 5.3              | 64            | 52 (79)           |
|                  |      |              | Sorafenib (62)    | 5.3              | 62            | 43 (69)           |
| AVOREN           | 2010 | 1st line     | Bevacizumab + IFN (327) | 3.5              | 61            | 222 (68)          |
|                  |      |              | Placebo + IFN (322) | 3.5              | 60            | 234 (73)          |
| CALGB 90206      | 2010 | 1st line     | Bevacizumab + IFN (369) | 5.0              | 61            | 269 (73)          |
|                  |      |              | IFN (363)         | 5.0              | 62            | 239 (66)          |
| Jonasch (2010)   | 2010 | 1st line     | Sorafenib + IFN (40) | 2.9              | 60.7          | 29 (72.5)         |
|                  |      |              | Sorafenib (40)    | 2.9              | 62.4          | 32 (80)           |
| Escudier (2009)  | 2009 | 1st line     | Sorafenib (97)    | 1.3              | 61.5          | 65 (67)           |
|                  |      |              | IFN (92)          | 1.3              | 61.8          | 52 (56.5)         |
| SUTENT           | 2009 | 1st line     | Sunitinib (375)   | 3.4              | 62            | 267 (71)          |
|                  |      |              | IFN (360)         | 3.4              | 59            | 269 (72)          |
| Global ARCC      | 2007 | 1st line     | Temsirolimus (209) | 2.5              | 58            | 139 (66)          |
|                  |      |              | IFN (207)         | 2.5              | 60            | 148 (71)          |
| JAVELIN Renal    | 2020 | 1st line     | Avelumab + Axitinib (442) | 2.8              | 62            | 316 (71.5)        |
| 101             |      |              | Sunitinib (444)   | 2.8              | 61            | 344 (77.5)        |
| Keynote-426      | 2019 | 1st line     | Pembrolizumab + Axitinib (432) | 2.0              | 62            | 308 (71.3)        |
|                  |      |              | Sunitinib (429)   | 2.0              | 61            | 320 (74.6)        |
| SWITCH           | 2015 | 1st/2nd line | Sunitinib (103)   | 4.2              | 65            | 135 (74)          |
|                  |      |              | Sorafenib (76)    | 4.2              | 64            | 139 (76)          |
| VEG10519         | 2013 | 1st/2nd line | Pazopanib (155)   | 3.8              | 59            | 198 (68)          |
|                  |      |              | Placebo (145)     | 3.8              | 60            | 109 (75)          |
| METEOR           | 2016 | 2nd line     | Cabozantinib (330) | 1.6              | 63            | 253 (77)          |
|                  |      |              | Everolimus (328)  | 1.6              | 62            | 241 (73)          |
| Motzer (2015)    | 2015 | 2nd line     | Lenvatinib (52)   | 2.3              | 64            | 39 (75)           |
|                  |      |              | Everolimus (50)   | 2.3              | 59            | 38 (76)           |
| ECOG PS, n (%) 0/1/2 | MSKCC prognostic risk, n (%) Low/intermediate/high | No. of metastatic sites, n (%) 1/2/3 | Previous nephrectomy, n (%) | Previous radio therapy, n (%) |
|-----------------------|-----------------------------------------------|----------------------------------|-----------------------------|-----------------------------|
| NR                    | NR                             | NR                              | NR                          | NR                          |
| 36 (46)/33 (42)/10 (13) | NR                             | NR                              | NR                          | NR                          |
| 36 (46)/32 (41)/10 (13) | NR                             | NR                              | NR                          | NR                          |
| 110 (57)/82 (43)/0 (0)  | 94 (49)/84 (44)/7 (4)          | NR                              | NR                          | NR                          |
| 55 (57)/41 (43)/0 (0)   | 53 (55)/40 (42)/2 (2)          | NR                              | NR                          | NR                          |
| 31 (60)/19 (36)/2 (4)   | 14 (27)/32 (62)/6 (12)         | NR                              | NR                          | NR                          |
| 26 (53)/20 (41)/2 (4)   | 12 (24)/27 (55)/9 (18)         | NR                              | NR                          | NR                          |
| NR                    | 123 (31)/230 (58)/47 (12)      | NR                              | NR                          | NR                          |
| NR                    | 114 (29)/237 (61)/40 (10)      | NR                              | NR                          | NR                          |
| NR                    | 70 (29)/132 (56)/35 (15)       | 73 (31)/164 (69)/0 (0)          | 159 (67)                    | NR                          |
| NR                    | 69 (30)/131 (56)/32 (14)       | 75 (32)/157 (67)/0 (0)          | 156 (67)                    | NR                          |
| 116 (45)/144 (55)/0 (0) | 70 (27)/173 (67)/17 (7)        | NR                              | NR                          | NR                          |
| 139 (54)/118 (46)/0 (0) | 87 (34)/160 (62)/10 (4)        | NR                              | NR                          | NR                          |
| NR                    | 151 (27)/322 (58)/67 (12)      | 117 (21)/204 (37)/235 (42)      | 459 (82)                    | 46 (8)                      |
| NR                    | 152 (27)/328 (59)/52 (9)       | 108 (20)/204 (37)/241 (44)      | 465 (84)                    | 42 (8)                      |
| NR                    | 36 (55)/27 (41)/3 (5)          | NR                              | 48 (73)                     | NR                          |
| NR                    | 34 (55)/24 (39)/4 (6)          | NR                              | 46 (74)                     | NR                          |
| NR                    | 87 (27)/183 (56)/29 (9)        | NR                              | 105 (32)                    | NR                          |
| NR                    | 93 (29)/180 (56)/25 (8)        | NR                              | NR                          | NR                          |
| 230 (62)/132 (36)/7 (2) | NR                             | NR                              | 312 (85)                    | 35 (9)                      |
| 227 (62)/133 (37)/3 (1) | NR                             | NR                              | 308 (85)                    | 38 (10)                     |
| 25 (62.5)/15 (37.5)/0 (0) | 20 (50)/18 (45)/2 (5)         | 14 (35)/20 (50)/6 (15)         | 39 (98)                     | NR                          |
| 25 (62.5)/15 (37.5)/0 (0) | 21 (52.5)/19 (47.5)/0 (0)      | 13 (33)/17 (42)/10 (25)        | 40 (100)                    | NR                          |
| 56 (57.7)/41 (42.3)/0 (0) | 52 (53.6)/44 (45.4)/1 (1)     | 9 (9.3)/88 (90.7)/0 (0)        | 95 (97.9)                   | 22 (22.7)                   |
| 49 (53.3)/43 (46.7)/0 (0) | 47 (51.1)/44 (47.8)/0 (0)      | 17 (18.5)/75 (81.5)/0 (0)      | 83 (90.2)                   | 52 (13)                     |
| 231 (62)/144 (38)/0 (0)  | 143 (38)/209 (56)/23 (6)       | 55 (15)/106 (28)/214 (58)      | 340 (91)                    | 53 (14)                     |
| 229 (61)/146 (39)/0 (0)  | 121 (34)/212 (59)/25 (7)       | 72 (19)/112 (30)/191 (51)      | 335 (89)                    | 54 (14)                     |
| NR                    | 0 (0)/64 (31)/145 (69)         | NR/166 (79)/NR                  | 139 (66)                    | NR                          |
| NR                    | 0 (0)/50 (24)/157 (76)         | NR/165 (80)/NR                  | 139 (67)                    | NR                          |
| NR                    | 96 (21.7)/283 (64)/51 (11.5)   | 181 (41)/148 (33.5)/102 (23.1) | 352 (79.6)                  | NR                          |
| NR                    | 96 (21.6)/276 (62.2)/71 (16)   | 174 (39.2)/151 (34)/103 (23.2) | 355 (80.0)                  | NR                          |
| NR                    | NR                             | 114 (26.4)/315 (72.9)          | 357 (82.6)                  | 41 (9.5)                    |
| NR                    | NR                             | 96 (22.4)/331 (77.2)           | 358 (83.4)                  | 40 (9.3)                    |
| 106 (60)/66 (38)/1 (1)  | 82 (45)/94 (51)/0 (0)          | 51 (29)/59 (34)/36 (20)        | NR                          | 23 (13)                     |
| 116 (66)/55 (31)/0 (0)  | 71 (39)/108 (59)/0 (0)         | 38 (21)/68 (38)/51 (29)        | NR                          | 16 (9)                      |
| 123 (42)/167 (58)/0 (0)  | 113 (39)/159 (55)/9 (3)        | 53 (18)/78 (27)/159 (55)       | 258 (89)                    | NR                          |
| 60 (41)/85 (59)/0 (0)   | 57 (39)/77 (53)/5 (3)          | 20 (14)/50 (34)/75 (52)        | 127 (88)                    | NR                          |
| 226 (68)/104 (32)/0 (0) | 150 (45)/139 (42)/41 (12)      | NR                             | 283 (86)                    | 110 (33)                    |
| 217 (66)/111 (34)/0 (0) | 150 (46)/135 (41)/43 (13)      | NR                             | 279 (85)                    | 108 (33)                    |
| 29 (56)/23 (44)/0 (0)   | 11 (21)/18 (35)/23 (44)        | 9 (17)/15 (29)/28 (54)         | 43 (83)                     | 11 (21)                     |
| 28 (56)/22 (44)/0 (0)   | 12 (24)/19 (38)/19 (38)        | 5 (10)/15 (30)/30 (60)         | 48 (96)                     | 11 (22)                     |

(Continues)
3.3 | Second-line therapy

Concerning PFS, cabozantinib was identified as the most effective treatment option (HR = 0.17, 95% CrI = 0.12-0.24; SUCRA = 96%; probability of being first rank = 0.70) in second-line therapy followed by lenvatinib (HR = 0.21, 95% CrI = 0.12-0.35; SUCRA = 86%) (Figure 3D; Table 3). Axitinib had the lowest HR of OS and discontinuation due to AE (HR = 0.54, 95% CrI = 0.40-0.71; HR = 0.98, 95% CrI = 0.42-1.97, respectively) (Figure 3E,F). Rank probability also showed the consistent results for OS and safety (SUCRA = 81% and 93%, respectively). The second choice was pazopanib in terms of OS (HR = 0.56, 95% CrI = 0.28-1.00; SUCRA = 76%) compared with placebo. The detailed point estimates and the probability that an intervention was better than a comparator for all pairwise comparisons are presented in Appendices S6-S11.

4 | DISCUSSION

This NMA is, to the best of our knowledge, the first study of the approved regimens, including the newer agents such as nivolumab, cabozantinib, lenvatinib and tivozanib, and nivolumab + ipilimumab, avelumab + axitinib and pembrolizumab + axitinib, for both the first-line and second-line treatment of mRCC. The fixed-effect Bayesian NMA was conducted to provide a structured means and rank of relative outcomes for marketed treatments that have not been compared in a head-to-head trial. Results from this NMA indicates cabozantinib, avelumab + axitinib, pembrolizumab + axitinib and nivolumab + ipilimumab regimens to be one of the most effective of the compared interventions, with the highest probability of being the best at improving both OS and PFS vs the other marketed regimens for previously untreated patients with RCC. However, the combination of pembrolizumab + axitinib and nivolumab + ipilimumab was not considered the safest therapy, whereas avelumab + axitinib and temsirolimus was the most tolerable treatment in the network, with the lowest risk of discontinuation due to severe AE in the first-line therapy. Although the combination therapies tend to have higher percentage of discontinuation due to AE, the therapy of avelumab + axitinib had lower frequency and percentage of patients who discontinued due to severe AE compared with axitinib (54.8% vs 75.7%), indicating that the severity of adverse events on the combination of avelumab + axitinib were consistent with the safety profiles of avelumab and axitinib of each monotherapy. Common adverse events included fatigue, hypertension, diarrhoea, abnormal liver function tests, anorexia and palmar-plantar erythrodysesthesia syndrome.

These results are consistent with previous NMA results. Although Wallis et al (2018) included atezolizumab, which was not approved to treat mRCC, they reported that cabozantinib and nivolumab + ipilimumab therapies are likely to be the preferred first-line agents for treating mRCC regarding increased PFS and OS, respectively (SUCRA: 91% and 48%). The CABOSUN trial presented that cabozantinib was superior to sunitinib because cabozantinib is an oral small-molecule inhibitor of tyrosine kinases, including MET, AXL and VEGFRs. High expression of MET or AXL is known to be associated with poor prognosis and resistance to VEGFR inhibitors in mRCC. In the JAVELIN Renal 101 and KEYNOTE-426 trial, the combination of an immune checkpoint inhibitor (avelumab or pembrolizumab) with a VEGF-targeted antiangiogenic therapy (axitinib) showed comparative enhanced benefit through complementary mechanisms of action compared with VEGFR monotherapy. Although nivolumab, a PD-1 immune checkpoint inhibitor antibody, was approved for the treatment of mRCC, ipilimumab, a monoclonal antibody cytotoxic T-lymphocyte protein 4 inhibitor, was approved for metastatic melanoma. Combination therapy with nivolumab plus ipilimumab has shown higher efficacy in multiple tumour types compared to agent alone. The combination showed antitumour activity with an objective response rate of 40% and a 2-year OS rate of 67 to 70%, depending on the dose,
In the second-line therapy, the advantage of cabozantinib and axitinib was particularly superior in improving OS and PFS, respectively. Especially, axitinib which also showed lowest risk of discontinuation due to AE. Another NMA evaluating second-line therapy also showed that axitinib was superior to pazopanib (HR = 0.64, 95% CrI = 0.42-0.96) and sorafenib (HR = 0.70, 95% CrI = 0.57-0.87) in terms of PFS.\textsuperscript{6} It should be noted that in the AXIS trial, although PFS remained significantly longer in axitinib group compared with the sorafenib group, axitinib failed to result in a prolongation in OS.\textsuperscript{57}

The choice of agent is important for the treatment for patients with mRCC, and many potential factors may contribute to treatment selection, including efficacy and safety profile, a patient’s tolerability to previous therapy, comorbidities and patient-specific circumstances.\textsuperscript{57} Although notable differences exist between the European Association of Urology (EAU), the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines, there are some consensus points between guidelines.\textsuperscript{64} The treatment with IL-2 and IFN-α generally

| ECOG PS, n (%) | MSKCC prognostic risk, n (%) | No. of metastatic sites, n (%) | Previous nephrectomy, n (%) | Previous radio therapy, n (%) |
|---------------|-------------------------------|-------------------------------|-------------------------------|-----------------------------|
| 0/1/2         | Low/intermediate/high         | 1/2/≥3                        |                               |                             |
| NR            | 145 (35)/201 (49)/64 (16)     | 68 (17)/341 (83)/0 (0)        | 364 (89)                      | NR                          |
| NR            | 148 (36)/203 (49)/60 (15)     | 71 (17)/338 (82)/0 (0)        | 359 (87)                      | NR                          |
| 103 (40)/150 (58)/4 (2) | 50 (19)/178 (69)/31 (12) | NR                            | 223 (86)                      | NR                          |
| 113 (45)/139 (55)/0 (0) | 44 (17)/177 (70)/32 (13) | NR                            | 219 (87)                      | NR                          |
| 195 (54)/162 (45)/1 (<1)  | 100 (28)/134 (37)/118 (33)  | NR                            | 329 (91)                      | 75.81 (21)                  |
| 200 (55)/160 (44)/0 (0)  | 101 (28)/130 (36)/120 (33)  | NR                            | 329 (91)                      | 72.4 (20)                   |
| NR            | 81 (29)/156 (56)/40 (14)      | 24 (9)/68 (25)/182 (66)       | 269 (97)                      | 85 (31)                     |
| NR            | 39 (28)/79 (57)/21 (15)       | 13 (9)/36 (26)/88 (63)        | 133 (96)                      | 38 (27)                     |
| 219 (49)/223 (49)/7 (2) | 233 (52)/218 (48)/0 (0) | 62 (14)/131 (29)/256 (57)    | 422 (94)                      | 124 (27)                    |
| 210 (46)/236 (52)/4 (1)  | 228 (50)/223 (49)/0 (0)      | 63 (14)/129 (29)/258 (57)    | 421 (93)                      | 108 (24)                    |

**TABLE** Comparison network of the included trials. A, Progression-free survival (PFS) in first-line therapy. B, Overall survival (OS) in first-line therapy. C, Discontinuation due to adverse events in first-line therapy. D, PFS in second-line therapy. E, OS in second-line therapy. F, Discontinuation due to adverse events in second-line therapy. Note. Each link represents at least one study and the widths of each link are proportional to the number of studies comparing the particular arms. The size of each node is proportional to the total sample size.
remain acceptable options; however, their use has been very limited because anti-VEGF agents and mTORIs have shown superiority to IL-2 or IFN-α. Although sunitinib, temsirolimus and everolimus are recommended in the first-line therapy, for the second-line therapy, sorafenib, axitinib and cabozantinib were unanimously recommended by EAU, ESMO and NCCN.

The feasibility of performing a valid NMA was assessed to synthesize direct and indirect evidence. The network was checked if available interventions are connected in a network and the quality of trials was validated using standard quality tools such as the Cochrane risk of bias. The meta-analyses were used to identify the heterogeneity of observed treatment effects for pairwise comparisons of sunitinib and everolimus with two trials. The assumption of consistency (agreement between direct and indirect sources of evidence) with closed loop of sorafenib-sunitinib-IFN-α was assessed, showing that there was no significant inconsistency. The complementary log-log link based on NICE guidelines was employed to adjust different follow-up times to generate more accurate estimates of the risk of discontinuation due to adverse events rate, because the included trials had various follow-up periods, ranging from 1.3 to 5 years.

Given the lack of comparative data from randomized head-to-head trials, indirect comparisons based on Bayesian NMA can provide valuable insights to clinicians and decision-makers (eg policymakers, reimbursement stakeholders and healthcare professionals/clinicians) on the relative efficacy of a range of treatments for RCC. The probabilistic interpretation of Bayesian results is appropriate for these purposes because that method naturally leads to a decision framework that supports decision making. For example, the posterior probability distribution allows calculations of the probability of which of the interventions are ranked the highest, which is more convenient to interpret the results than classical P-values used in the frequentist approach.

There were limitations that should be carefully considered when the results are interpreted. The current NMA compared not...
| Intervention                        | SUCRA, mean (95% CrI) | Mean of rank, mean (95% CrI) | Probability of being 1st rank, mean | Probability that the intervention is better than Placebo, mean |
|------------------------------------|-----------------------|------------------------------|-------------------------------------|---------------------------------------------------------------|
| **Progression-free survival**      |                       |                              |                                     |                                                               |
| Cabozantinib                       | 0.91 (0.63-1.00)      | 2.47 (1-7)                   | 0.42                                | 1.00                                                          |
| Avelumab + axitinib                | 0.90 (0.75-1.00)      | 2.62 (1-5)                   | 0.20                                | 1.00                                                          |
| Pembrolizumab + axitinib           | 0.90 (0.75-1.00)      | 2.64 (1-5)                   | 0.21                                | 1.00                                                          |
| Nivolumab + ipilimumab             | 0.81 (0.63-0.94)      | 4.05 (2-7)                   | 0.02                                | 1.00                                                          |
| Pazopanib + everolimus             | 0.71 (0.25-1.00)      | 5.62 (1-13)                  | 0.11                                | 1.00                                                          |
| Axitinib                           | 0.60 (0.25-0.94)      | 7.41 (2-13)                  | 0.01                                | 1.00                                                          |
| Sunitinib                          | 0.59 (0.44-0.75)      | 7.52 (5-10)                  | 0.00                                | 1.00                                                          |
| Tivozanib                          | 0.57 (0.31-0.81)      | 7.89 (4-12)                  | 0.00                                | 1.00                                                          |
| Pazopanib                          | 0.53 (0.31-0.69)      | 8.59 (6-12)                  | 0.00                                | 1.00                                                          |
| Sorafenib + IFN                    | 0.50 (0.06-0.94)      | 8.93 (2-16)                  | 0.02                                | 0.99                                                          |
| Bevacizumab + IFN                  | 0.41 (0.25-0.69)      | 10.46 (6-13)                 | 0.00                                | 1.00                                                          |
| Sorafenib                          | 0.32 (0.19-0.50)      | 11.91 (9-14)                 | 0.00                                | 1.00                                                          |
| Temsirolium + bevacizumab          | 0.31 (0.19-0.63)      | 12.06 (7-14)                 | 0.00                                | 1.00                                                          |
| Everolimus                          | 0.25 (0.13-0.44)      | 13.04 (10-15)                | 0.00                                | 1.00                                                          |
| IFN                                 | 0.11 (0.06-0.19)      | 15.26 (14-16)                | 0.00                                | 0.95                                                          |
| Placebo + IFN                      | 0.08 (0.00-0.19)      | 15.68 (14-17)                | 0.00                                | 0.90                                                          |
| Placebo                            | 0.01 (0.00-0.13)      | 16.83 (15-17)                | 0.00                                | NA                                                            |
| **Overall survival**               |                       |                              |                                     |                                                               |
| Pembrolizumab + axitinib           | 0.97 (0.81-1.00)      | 1.53 (1-4)                   | 0.65                                | 0.99                                                          |
| Nivolumab + ipilimumab             | 0.89 (0.63-1.00)      | 2.70 (1-7)                   | 0.20                                | 0.97                                                          |
| Avelumab + axitinib                | 0.73 (0.38-0.94)      | 5.28 (2-11)                  | 0.01                                | 0.92                                                          |
| Cabozantinib                       | 0.69 (0.13-1.00)      | 5.93 (1-15)                  | 0.05                                | 0.90                                                          |
| Pazopanib + everolimus             | 0.65 (0.06-1.00)      | 6.59 (1-16)                  | 0.07                                | 0.88                                                          |
| Temsirolium                         | 0.62 (0.25-0.88)      | 7.14 (3-13)                  | 0.00                                | 0.87                                                          |
| Pazopanib                          | 0.59 (0.25-0.81)      | 7.56 (4-13)                  | 0.00                                | 0.88                                                          |
| Sorafenib + IL-2                   | 0.56 (0.06-0.94)      | 8.01 (2-16)                  | 0.02                                | 0.83                                                          |
| Axitinib                           | 0.46 (0.06-0.88)      | 9.64 (3-16)                  | 0.00                                | 0.79                                                          |
| Sorafenib                          | 0.45 (0.13-0.75)      | 9.75 (5-15)                  | 0.00                                | 0.80                                                          |
| Sunitinib                          | 0.44 (0.19-0.69)      | 9.94 (6-14)                  | 0.00                                | 0.82                                                          |
| Temsirolium + bevacizumab          | 0.40 (0.06-0.81)      | 10.67 (4-16)                 | 0.00                                | 0.77                                                          |
| Bevacizumab + IFN                  | 0.39 (0.13-0.75)      | 10.72 (5-15)                 | 0.00                                | 0.77                                                          |
| Placebo                            | 0.19 (0.00-0.88)      | 14.03 (3-17)                 | 0.01                                | NA                                                            |
| Tivozanib                          | 0.19 (0.00-0.63)      | 14.00 (7-17)                 | 0.00                                | 0.62                                                          |
| IFN                                 | 0.17 (0.00-0.38)      | 14.23 (11-17)                | 0.00                                | 0.65                                                          |
| Placebo + IFN                      | 0.11 (0.00-0.44)      | 15.26 (10-17)                | 0.00                                | 0.56                                                          |
| **Discontinuation due to adverse events** |                       |                              |                                     |                                                               |
| Avelumab + axitinib                | 0.87 (0.67-1.00)      | 2.99 (1-6)                   | 0.15                                | 0.51                                                          |
| Placebo + IFN                      | 0.84 (0.53-1.00)      | 3.39 (1-8)                   | 0.24                                | NA                                                            |
| Temsirolium                         | 0.80 (0.47-1.00)      | 3.94 (1-9)                   | 0.22                                | 0.45                                                          |
| Sorafenib                          | 0.78 (0.60-1.00)      | 4.29 (1-7)                   | 0.04                                | 0.36                                                          |
| Tivozanib                          | 0.74 (0.27-1.00)      | 4.92 (1-12)                  | 0.15                                | 0.36                                                          |
| Everolimus                          | 0.70 (0.40-1.00)      | 5.52 (1-10)                  | 0.03                                | 0.24                                                          |
| Cabozantinib                       | 0.56 (0.13-1.00)      | 7.57 (1-14)                  | 0.03                                | 0.15                                                          |

(Continues)
### TABLE 3
Surface under the cumulative ranking (SUCRA) and ranking of interventions in second-line therapy

| Intervention           | SUCRA, mean (95% CrI) | Mean of rank, mean (95% CrI) | Probability of being 1st rank, mean | Probability that the Intervention is better than Placebo, mean |
|------------------------|-----------------------|------------------------------|-------------------------------------|---------------------------------------------------------------|
| **Progression-free survival** |                       |                              |                                     |                                                               |
| Cabozantinib           | 0.96 (0.78-1.00)      | 1.34 (1-3)                   | 0.70                                | 1.00                                                          |
| Lenvatinib             | 0.86 (0.56-1.00)      | 2.28 (1-5)                   | 0.24                                | 1.00                                                          |
| Sunitinib              | 0.76 (0.44-1.00)      | 3.13 (1-6)                   | 0.06                                | 1.00                                                          |
| Nivolumab              | 0.63 (0.33-0.78)      | 4.36 (3-7)                   | 0.00                                | 1.00                                                          |
| Axitinib               | 0.60 (0.33-0.89)      | 4.58 (2-7)                   | 0.00                                | 1.00                                                          |
| Everolimus             | 0.46 (0.22-0.67)      | 5.86 (4-8)                   | 0.00                                | 1.00                                                          |
| Temsirolimus           | 0.36 (0.22-0.56)      | 6.79 (5-8)                   | 0.00                                | 1.00                                                          |
| Sorafenib              | 0.22 (0.11-0.33)      | 8.04 (7-9)                   | 0.00                                | 1.00                                                          |
| Pazopanib              | 0.15 (0.11-0.44)      | 8.63 (6-9)                   | 0.00                                | 1.00                                                          |
| Placebo                | 0.00 (0.00-0.00)      | 10.00 (10-10)                | 0.00                                | NA                                                            |
| **Overall survival**   |                       |                              |                                     |                                                               |
| Axitinib               | 0.81 (0.50-1.00)      | 2.52 (1-5)                   | 0.25                                | 1.00                                                          |
| Pazopanib              | 0.76 (0.13-1.00)      | 2.89 (1-8)                   | 0.38                                | 0.98                                                          |
| Cabozantinib           | 0.75 (0.38-1.00)      | 3.03 (1-6)                   | 0.13                                | 1.00                                                          |
| Lenvatinib             | 0.68 (0.13-1.00)      | 3.54 (1-8)                   | 0.20                                | 0.96                                                          |
| Nivolumab              | 0.63 (0.25-1.00)      | 4.00 (1-7)                   | 0.04                                | 0.99                                                          |
| Sorafenib              | 0.42 (0.25-0.75)      | 5.65 (3-7)                   | 0.00                                | 0.99                                                          |
| Everolimus             | 0.25 (0.00-0.50)      | 7.00 (5-9)                   | 0.00                                | 0.83                                                          |
| Temsirolimus           | 0.11 (0.00-0.38)      | 8.14 (6-9)                   | 0.00                                | 0.48                                                          |
| Placebo                | 0.10 (0.00-0.25)      | 8.23 (7-9)                   | 0.00                                | NA                                                            |
| **Discontinuation due to adverse events** |                       |                              |                                     |                                                               |
| Axitinib               | 0.93 (0.75-1.00)      | 1.59 (1-3)                   | 0.56                                | 0.60                                                          |
| Placebo                | 0.89 (0.63-1.00)      | 1.90 (1-4)                   | 0.36                                | NA                                                            |
| Sorafenib              | 0.65 (0.38-0.88)      | 3.82 (2-6)                   | 0.00                                | 0.07                                                          |
| Sunitinib              | 0.65 (0.25-1.00)      | 3.77 (1-7)                   | 0.05                                | 0.17                                                          |
| Nivolumab              | 0.55 (0.38-0.88)      | 4.58 (2-6)                   | 0.02                                | 0.05                                                          |
| Temsirolimus           | 0.37 (0.00-0.63)      | 6.01 (4-9)                   | 0.00                                | 0.00                                                          |
| Everolimus             | 0.25 (0.13-0.50)      | 6.98 (5-8)                   | 0.00                                | 0.00                                                          |
| Cabozantinib           | 0.18 (0.00-0.50)      | 7.58 (5-9)                   | 0.00                                | 0.00                                                          |
| Lenvatinib             | 0.03 (0.00-0.38)      | 8.77 (6-9)                   | 0.00                                | 0.00                                                          |

*For discontinuation due to adverse events, placebo + interferon (IFN).*
all interventions in mRCC-related clinical trials. The intervention included only agents that were approved by the FDA or EMA for the treatment of mRCC. For example, although there were RCTs with atezolizumab and cediranib for patients with mRCC, they are not approved for mRCC as of June 2020. This study analysed relative efficacy and safety among comprehensive currently approved medications for patients with mRCC. Only RCTs were accepted in the analyses, and it was assumed that baseline patient characteristics were well balanced between groups. However, the randomization cannot always prevent imbalances between two groups and all NMAAs are affected by the quality of selected trials. Concerning statistical methodology, there was only one randomized trial per a pairwise comparison suitable for indirect analysis, which may reduce the statistical power to find significant differences. Although the feasibility was assessed, some heterogeneity in baseline characteristics still existed among RCTs analysed. The Cochrane risk of bias showed that CABOSUN and COMPAZ trials did not have a double-blind design. Further studies may need to consider subgroup analyses, allowing evaluation of the impact of some of the differences in patient characteristics, including treatment effect modifiers.

5 | WHAT IS NEW AND CONCLUSION

This study provides the updated insight stakeholders on the efficacy and safety of a range of approved treatments for RCC. The results of NMA showed that cabozantinib and combination therapy of axelimab + axitinib, pembrolizumab + axitinib and/or nivolumab + ipilimumab are likely to be the preferred options for the first-line therapy based on PFS and OS, whereas the regimen of cabozantinib and axitinib was superior to other treatments for the second-line therapy. Regarding safety, axelimab + axitinib, temsirolimus and axitinib were considered preferred treatment options in the first-line and second-line therapies.

CONFLICT OF INTEREST

All authors have no conflicts of interest to disclose.

AUTHORS’ CONTRIBUTIONS

JHH: developed the study design, conducted statistical analyses, drafted the initial manuscript and approved the final manuscript as submitted. CP: performed a systematic literature review, drafted the initial manuscript and approved the final manuscript as submitted. SG: performed a systematic literature review and approved the final manuscript as submitted. S-KP: performed a systematic literature review and approved the final manuscript as submitted. KLR: critically reviewed and revised the manuscript and approved the final manuscript as submitted. MZ: critically reviewed and revised the manuscript and approved the final manuscript as submitted.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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