Contents of Appendix files, figures and tables

Appendix file 1: supplementary method of meta-analysis

1.1 Search strategies for PubMed, EMBASE and Cochrane database

PubMed: 255 results

("pembrolizumab" [Supplementary Concept] OR "lambrolizumab"[Title/Abstract] OR "Keytruda"[Title/Abstract] OR "MK-3475"[Title/Abstract] OR "nivolumab"[Supplementary Concept] OR "MDX-1106"[Title/Abstract] OR "ONO-4538"[Title/Abstract] OR "BMS-936558"[Title/Abstract] OR "Opdivo"[Title/Abstract] OR "atezolizumab"[Supplementary Concept] OR "anti-PDL1"[Title/Abstract] OR "MPDL3280A"[Title/Abstract] OR "Tecentriq"[Title/Abstract] OR "RG7446"[Title/Abstract] OR "RG-7446"[Title/Abstract] OR "Durvalumab" [Supplementary Concept] OR "Durvalumab" [Title/Abstract] OR "MEDI4736"[Title/Abstract] OR "MEDI-4736"[Title/Abstract] OR "Imfinzi"[Title/Abstract] OR "Avelumab"[Supplementary Concept] OR " Avelumab "[Title/Abstract] OR "Bavencio"[Title/Abstract] OR "MSB0010718C"[Title/Abstract] OR "anti-PD1"[Title/Abstract] OR "PD-1"[Title/Abstract] OR "Programmed Death 1"[Title/Abstract] OR "Programmed Cell Death 1 Receptor"[Title/Abstract] OR "PD 1"[Title/Abstract] OR "PD1"[Title/Abstract] OR "Programmed Death-Ligand 1"[Title/Abstract] OR "PD-L1"[Title/Abstract] OR "programmed cell death 1 ligand 1 protein"[Title/Abstract] OR "PD L1"[Title/Abstract] OR "PDL1"[Title/Abstract])
AND ((renal[Title/Abstract] OR Kidney[Title/Abstract]) AND ((RCC[Title/Abstract] OR mRCC[Title/Abstract] OR aRCC[Title/Abstract]OR RCC[Title/Abstract]) OR "MALIGNANC"[Title/Abstract] OR "TUMO"[Title/Abstract] OR "NEOPLAS"[Title/Abstract] OR "carcinoma"[Title/Abstract] OR "ADENOCARCINOMA"[Title/Abstract]) OR "Carcinoma, Renal Cell"[Mesh] OR "Kidney Neoplasms"[Mesh])
AND (("clinical trials as topic"[MeSH Terms] OR "trial"[Title/Abstract] OR "study"[Title/Abstract]))

EMbase: 135 results
('pembrolizumab'/exp OR 'lambrolizumab':ab,ti OR 'Keytruda':ab,ti OR 'MK-3475':ab,ti OR 'nivolumab'/exp OR 'MDX-1106':ab,ti OR 'ONO-4538':ab,ti OR 'BMS-936558':ab,ti OR 'Opdivo':ab,ti OR 'atezolizumab'/exp OR 'anti-PDL1':ab,ti OR 'MPDL3280A':ab,ti OR ' Tecentriq':ab,ti OR 'RG7446':ab,ti OR 'RG-7446':ab,ti OR 'Durvalumab':ab,ti OR 'MEDI4736':ab,ti OR 'MEDI-4736':ab,ti OR 'Imfinzi':ab,ti OR 'Avelumab':ab,ti OR 'MSB0010718C':ab,ti OR 'Bavencio':ab,ti OR 'anti-PD1':ab,ti OR 'PD-1':ab,ti OR 'Programmed Death 1':ab,ti OR 'Programmed Cell Death 1 Receptor':ab,ti OR 'PD-1':ab,ti OR 'PD1':ab,ti OR 'Programmed Death-Ligand 1':ab,ti OR 'PD-L1':ab,ti OR 'programmed cell death 1 ligand 1 protein':ab,ti OR 'PD L1' :ab,ti OR 'PDL1':ab,ti)
AND (('Renal Cell Carcinoma'/exp OR (('renal':ab,ti OR 'kidney':ab,ti) AND (('RCC':ab,ti OR 'mRCC':ab,ti OR 'aRCC':ab,ti) OR 'carcinoma':ab,ti OR 'ADENOCARCINOMA':ab,ti OR 'Tumor':ab,ti OR 'NEOPLASma':ab,ti OR 'MALIGNANCy':ab,ti))))

AND (‘randomized controlled trial’/exp)

Cochrane: 290 results, 278 trials
#1 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees
#2 MeSH descriptor: [Kidney Neoplasms] explode all trees
#3 (“renal” OR “Kidney”) AND ("carcinoma" OR "ADENOCARCINOMA" OR "Tumor" OR "Cancer" OR "NEOPLASma" OR "MALIGNANCy" OR "mRCC" OR "aRCC" OR "RCC")
#4 "pembrolizumab" or "lambrolizumab" or "Keytruda" or "MK-3475" or "nivolumab" or "MDX-1106" or "ONO-4538" or "BMS-936558" or "Opdivo" or "atezolizumab" or "anti-PDL1" or "MPDL3280A" or "Tecentriq" or "RG7446" or "RG-7446" or "Durvalumab" or "Avelumab" or "Bavencio" or "MSB0010718C" or "anti-PD1" or "PD-1"
or "Programmed Death 1" or "Programmed Cell Death 1 Receptor" or "PD 1" or "PD1" or "Programmed Death-Ligand 1" or "PD-L1" or "programmed cell death 1 ligand 1 protein" or "PD L1" or "PDL1"
#5 (#1 OR #2 OR #3) AND #4

Appendix file 2: supplementary method 1 of cost-effectiveness analysis

2. Materials and Methods

2.1. Model structure

A Markov model was developed to evaluate the costs and health outcomes of treating aRCC with sunitinib, atezolizumab plus bevacizumab, nivolumab plus ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib. The model included the following three discrete health states reflecting different characteristics of the disease: PFS, progressed survival (PS) and death (appendix figure 5). The time in each health state was estimated using partition survival methods (i.e., area under the survival curves). Because the treatment schedules in the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials were arranged by using week as the unit, the cycle length of the Markov model was set to be one week [1-4]. The time horizon was 10 years in the base-case analysis, and the initial health state for all of the patients was PFS [5]. The impact of the time horizon was evaluated in the sensitivity analysis. During each one-week cycle, the patients either remained in their assigned health state or progressed to a new health state. It was assumed that patients cannot return to previous health states. The following hypothetical patient demographics when entering the model matched those of the patients in the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials: 62 years old and 72.8% male, with previously untreated aRCC with a clear-cell component. [1] Model development and data analysis were performed in the R statistical environment (version 3.5.2; R Development Core Team, Vienna, Austria).

The main outcomes were expected life years (LYs), QALYs and cost. Cost and QALYs were discounted at an annual rate of 3% in the US. The costs are shown in 2017 US dollars. ICERs were examined and are presented as cost per additional QALY gained. According to the published literature, the cost-effectiveness threshold in the US was $150,000 [6,7].

2.1. Clinical data

Clinical efficacy and safety data were obtained from the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials [1-4]. By using the method described by Guyot *et al* [8], we replicated the individual PFS and OS data of the overall population in the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials after the Kaplan–Meier curves were extracted and digitized with the GetData Graph Digitizer version 2.26. Virtual patient-level data comprised event and censor times and were equal in number to the initial number at risk, which was closely reproduced the digitized Kaplan–Meier curves. The PFS and OS plots created by using the virtual patient-level data and the predicted curves by using parametric survival models are shown in appendix figures 6-9.

Due to the comparable characteristics of the patients and the absence of a significant difference in PFS in the sunitinib armbetween the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials, we pooled the virtual patient-level data in the sunitinib arm of the four clinical trials and fitted the PFS and OS data by the log-logistic distribution according to the results of the goodness of fit measured by the Akaike information criterion (AIC) statistic (appendix figure 10). The estimated parameters of the log-logistic distribution are shown in appendix table 5. We estimated the OS rates of atezolizumab plus bevacizumab, nivolumab plus ipilimumab,

pembrolizumab plus axitinib, and avelumab plus axitinib strategies by multiplying the survival probabilities in the sunitinib treatment and the HRs of ICI regimens against sunitinib treatment in the overall population, which were derived from the results of our network meta-analysis (Figure 1 and 2 in the article).

In subgroup analysis for PD-L1-positive and -negative patients, the PFS and OS probabilities of PD-L1-positive and -negative patients in the atezolizumab plus bevacizumab, nivolumab plus ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib arms were also calculated by multiplying the survival probabilities in the sunitinib treatment and the HRs of ICI regimens against sunitinib treatment in the PD-L1-positive and –negative tumours, respectively. These HRs for PFS and OS in PD-L1-positive and -negative patients were derived from the results of our network meta-analysis (Figure 1 and 2 in the article). It was assumed that the PFS probabilities of sunitinib treatment in PD-L1-positive and negative patients is similar with the overall population because there were no significant differences in PFS between PD-L1-positive patients and the overall population in the IMmotion 151 and JAVELIN Renal 101 trials (appendix figures 11A , 11B and 11C). However, because a significant difference in OS between PD-L1-positive and negative patients in the CheckMate 214 trial (appendix figure 11D) was observed, we estimated the OS of the sunitinib treatment in the PD-L1-positive/negative tumours by multiplying the survival probabilities in the overall population and the HRs of positive/negative tumours against the overall population. Based on the virtual patient-level data of CheckMate 214 and IMmotion 151 trial, the estimated HRs of sunitinib treatment of PD-L1-positive and negative patients versus overall population were 1.20 (95% CI: 0.62 - 1.12) and 0.90 (95% CI: 0.88 -1.41), respectively.

The durations of the PFS and progression of disease (PD) phases in four competing strategies were calculated using the area under the PFS and OS survival curves. The difference between the OS and PFS estimated from the survival distribution models was used to calculate the probability from PFS to death. [9] After the disease progressed, the proportion of patients who received second-line active treatment was collected from the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials [1-4].

2.3. Cost and utility estimates

This analysis adopted the third-party payer perspective in the US, which considered only direct medical costs, including first- and second-line treatment, management of treatment-related serious adverse events (SAEs), routine follow-ups and monitoring, best supportive care (BSC) and terminal care (table 1). The costs were reported in 2017 US dollars. The costs associated with health care services were inflated to 2017 values according to the US consumer price index [10].

Based on the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials, sunitinib was prescribed at a dose of 50 mg/day for 4 weeks followed by 2 weeks without treatment [1-4]. The intensity of sunitinib was 83.9% (range: 67% - 100%) [2,11]. Nivolumab and ipilimumab were administered intravenously at doses of 3 mg/kg and 1 mg/kg, respectively, every 3 weeks for four doses (induction phase), followed by nivolumab monotherapy at a dose of 3 mg/kg every 2 weeks (maintenance phase). Avelumab was administered at a dose of 10 mg/kg every 2 weeks, and pembrolizumab was administered intravenously at a dose of 200 mg once every 3 weeks. Axitinib was administered orally at a starting dose of 5 mg twice daily on a continuous dosing schedule. Atezolizumab and bevacizumab were administered intravenously at a dose of 1200 mg and 15 mg/kg every 3 weeks. To calculate the doses of the agents based on body weight, we assumed a

typical patient weighed 71.4 kg in the US, and the range (29-112 kg) was used in the sensitivity analysis[12-14]. Based on previous reports, the maximum treatment duration of nivolumab plus ipilimumab was two years[13,15]. Because the median relative dose intensity of sunitinib and axitinib was 83.9% and 89.4% as JAVELIN Renal 101 trial reported, we estimated the daily cost of sunitinib and axitinib based on the fully dose. The prices of sunitinib, pembrolizumab, avelumab, nivolumab, ipilimumab, atezolizumab, bevacizumab and axitinib in the US (average wholesale price) were collected from public databases and the literature [16]. Other cost data were collected from the published literature[14-26].

The analysis included the following grade 3/4 AEs that had notably different probabilities between the arms of the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials: fatigue, hypertension, anaemia, palmar–plantar erythrodysesthesia and thrombocytopenia[1-4]. The recommended management of AEs could be found in the clinical guidelines[27,28]. The costs of managing AEs per event in the US were extracted from the literature[19-21,25,26,29-31].

The mean health utility scores for the PFS and PD states were derived from the published literature (table 1) [14,23,32,33]. The disutility values due to grade 1/2 and 3/4 AEs were included in this analysis[32].

2.4. Sensitivity and Scenario analysis

One-way and probabilistic sensitivity analyses were used to test the uncertainty in the model. In the one-way sensitivity analyses, to identify key model input parameters that had substantial impact on the model outcome, the relevant parameters were individually adjusted to their respective low and high values, which are listed and illustrated in table 1. The ranges of the parameters used in the one-way sensitivity analyses were obtained from the published literature; when reported data were not available, a range ±25% of the base-case value was used. An assumed 50% discount of the price of sunitinib, ipilimumab and nivolumab was used for one-way sensitivity analyses. The results of the one-way sensitivity analyses are presented in a tornado diagram. For the PSAs, the parameters were sampled using the Monte Carlo method to run 1,000 replicated outcomes. Based on the ISPOR-SMDM Modeling Good Research Practices Task Force report on model parameter estimation and uncertainty, the values of the input parameters were sampled from lognormal distributions for costs and relative risks, and from β distributions for utility values and probabilities or proportions with an assumed standard deviation of 25% from the mean values[34]. The price of sunitinib, ipilimumab and nivolumab were fixed in the PSA since they are branded drugs. Cost-effectiveness acceptability curves were generated to present the probabilities of cost-effectiveness.

In the scenario analysis, we checked the impact of an updated nivolumab dosing schedule, a single 480 mg iv. dose every 4 weeks [35] on the economic outcomes. The impact caused by the time horizon would also be tested.

To enhance the transferability of the findings, we also evaluated the cost-effectiveness of ICI regimens in the setting of a representative European country (United Kingdom) from the National Health Service perspective and a middle-income country (China) from the health care perspectives by using scenario analysis. The costs are also shown in 2017 US dollars (appendix table 6). GBP and the Chinese Yuan were converted into US dollars by using the following exchange formulas: 1US $ = GBP 0.7075, and 1US $ = CNY 6.8. The UK costs associated with health care services were inflated to 2017 values according to the UK consumer price index [22]. As in a previous study, we took the average increase in the index for the previous three years when the local index was

unavailable [22]. Because the Chinese health care costs were controlled by the government and kept stable, the Chinese costs were not inflated in the current analysis. The cost and QALYs were discounted at an annual rate of 3.5% in the United Kingdom and 5% in China [13,36]. ICERs were examined and presented as cost per additional QALY gained. According to the published literature, the cost-effectiveness thresholds in the UK and China were $65,000 and $27,351 (3× the per capita gross domestic product of China in 2017), respectively[13,36].

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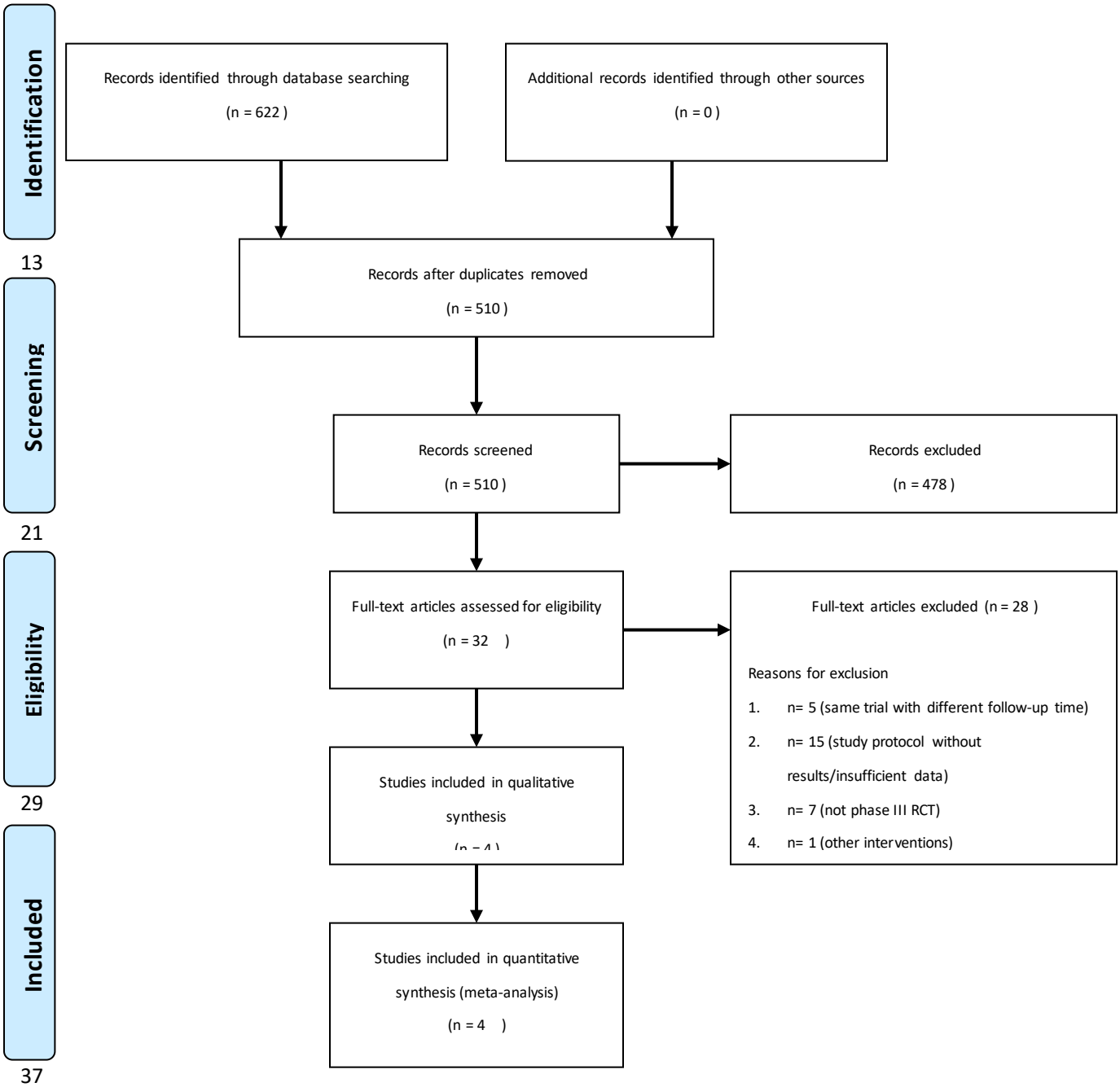
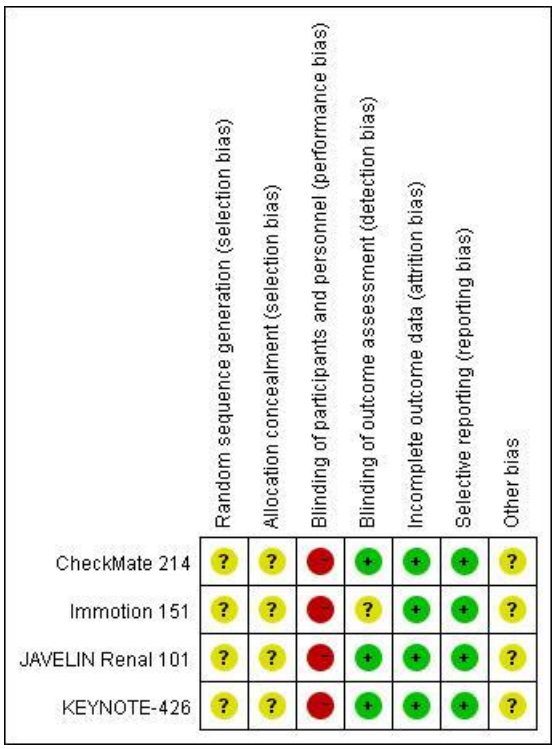
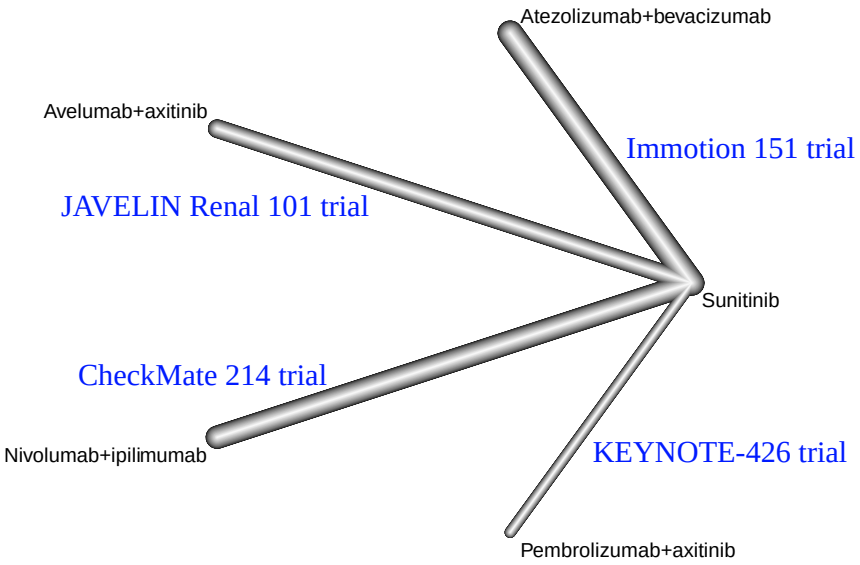


Appendix Figure 1: Flow chart of evidence acquisition.

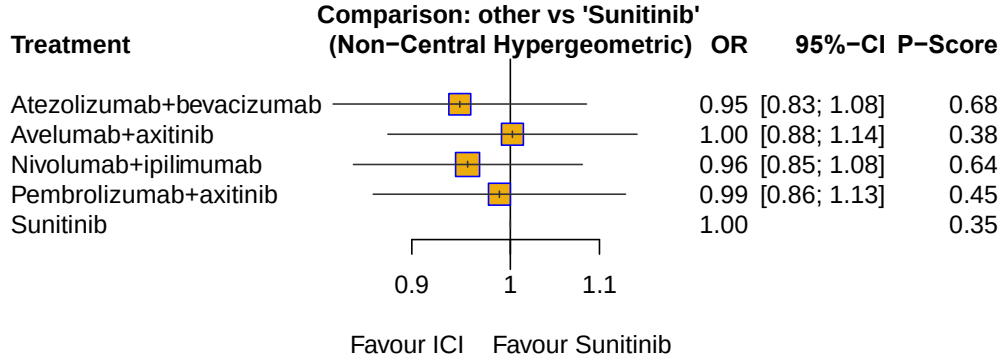


Appendix Figure 2: Network plot of evidence of all trials.

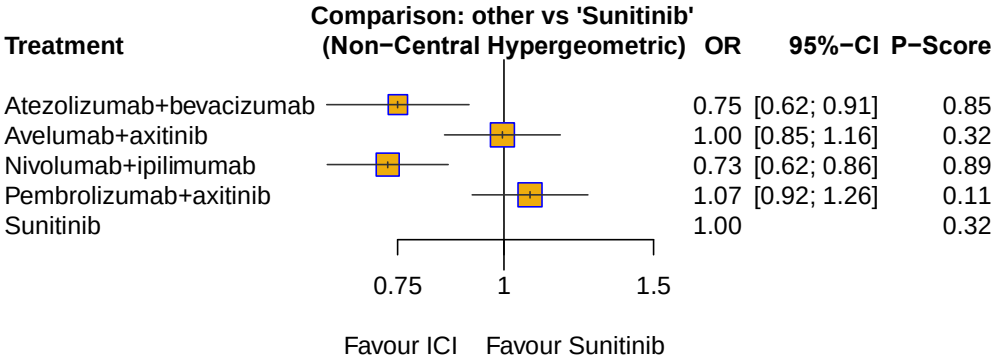


Appendix Figure 3: Network plot of evidence of all trials.

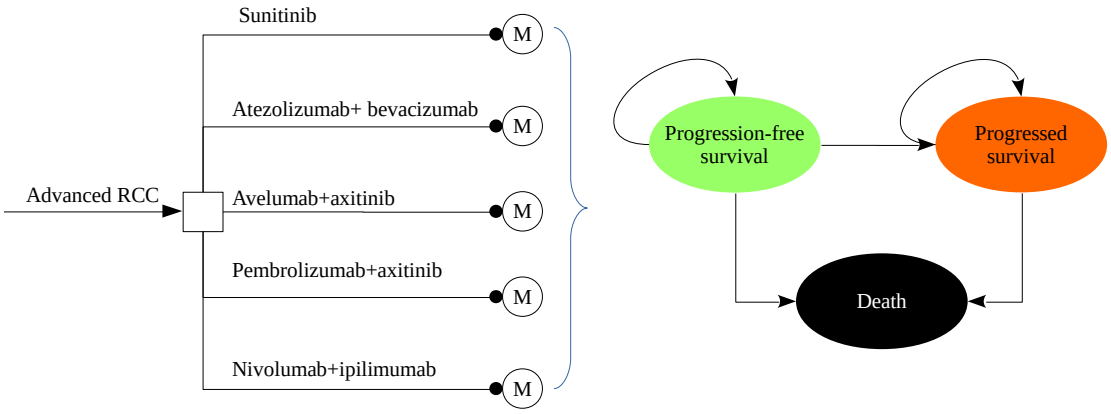
A.



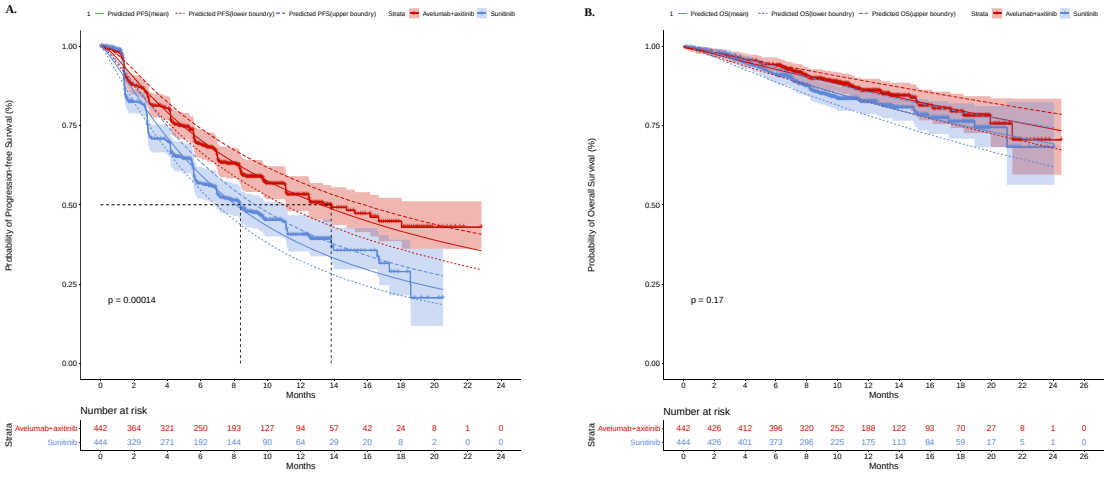
B.



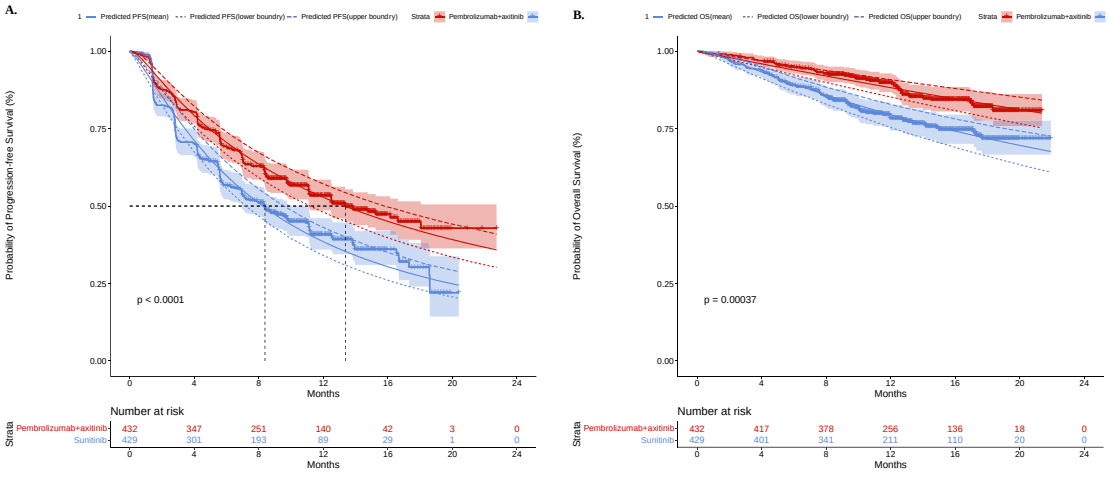
Appendix Figure 4: The forest plots of any ADRs (A) and ADRs (B) grade≥3 in the comparisons of four ICI regimens versus sunitinib treatment.



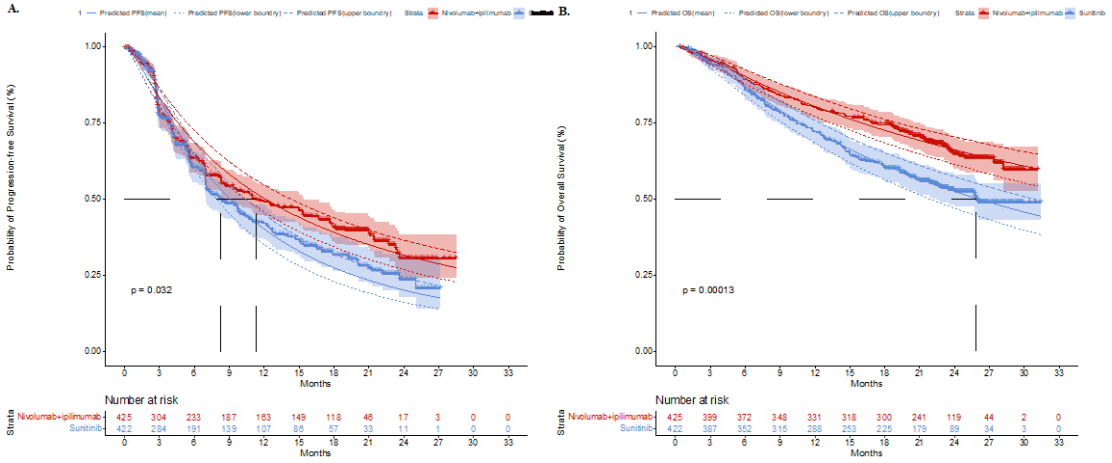
Appendix Figure 5: Model structure for cost-effectiveness analysis.



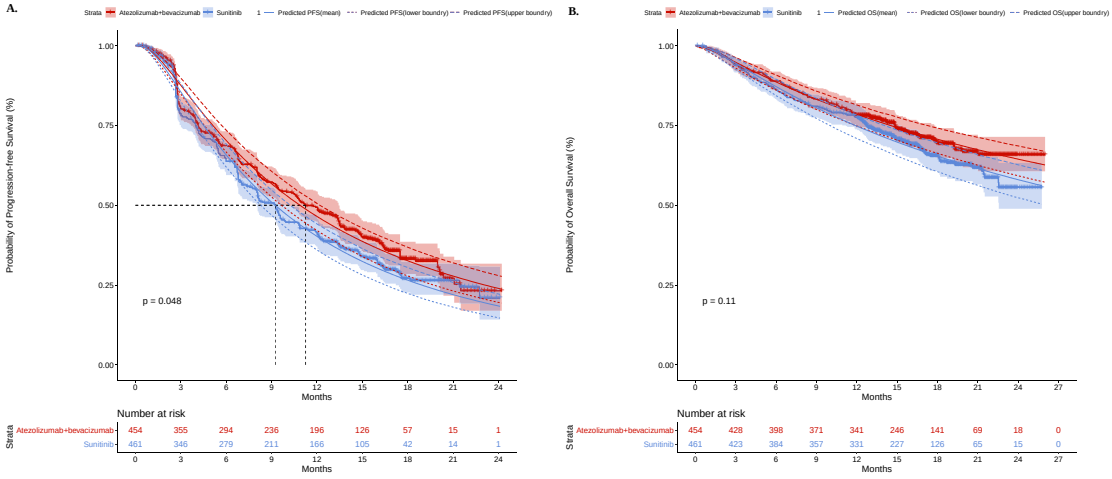
Appendix Figure 6: The replicated Kaplan–Meier PFS (A) and OS (B) curves of Avelumab+axitinib (red) and Sunitinib treatments (blue) in JAVELIN Renal 101 trial. The smooth lines indicated the survival curves predicting their corresponding best survival distributions (The distribution information showed in appendix Table 5). The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI.



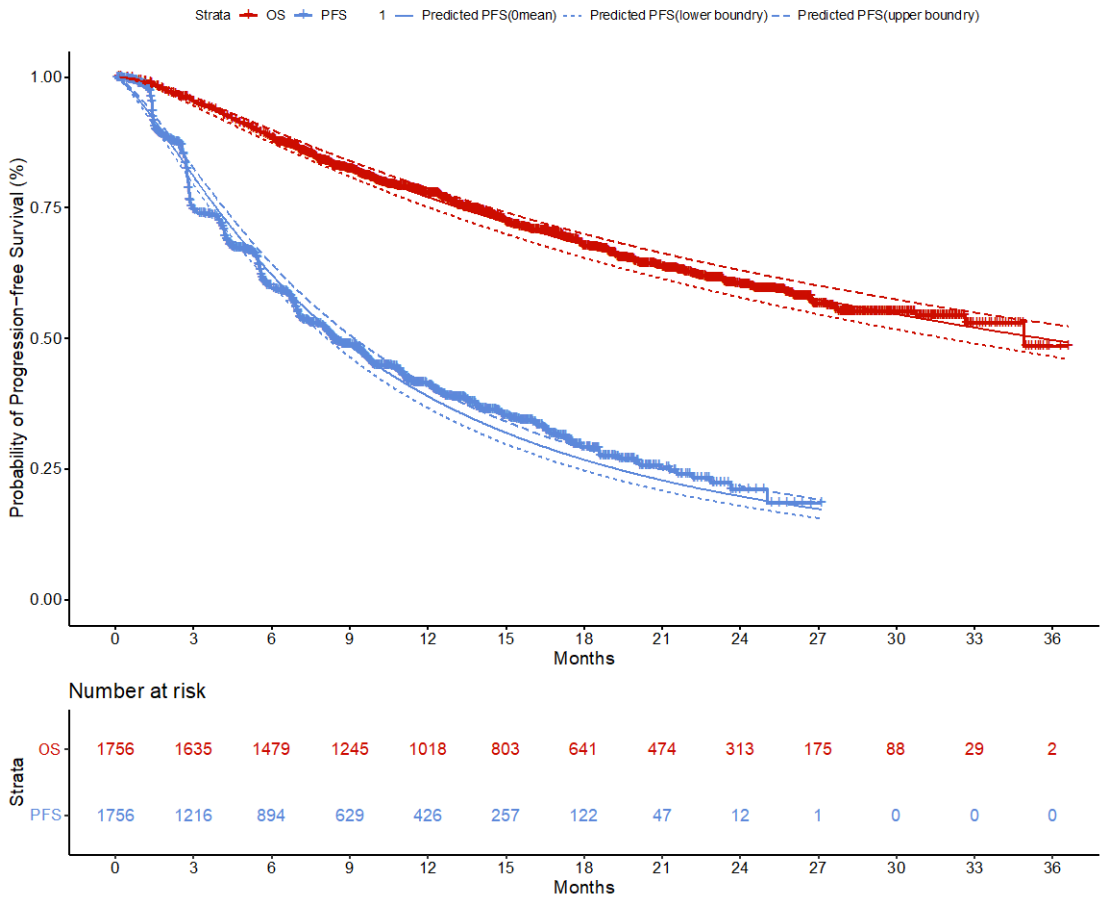
Appendix Figure 7: The replicated Kaplan–Meier PFS (A) and OS (B) curves of Pembrolizumab+axitinib (red) and Sunitinib treatments (blue) in KEYNOTE-426 trial. The smooth lines indicated the survival curves predicting their corresponding best survival distributions (The distribution information showed in appendix Table 5). The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI.



Appendix Figure 8: The replicated Kaplan–Meier PFS (A) and OS (B) curves of Nivolumab+ipilimumab (red) and Sunitinib treatments (blue) in CheckMate 214 trial. The smooth lines indicated the survival curves predicting their corresponding best survival distributions (The distribution information showed in appendix Table 5). The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI.

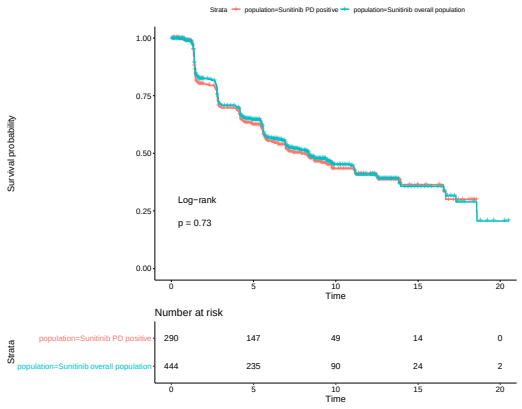


Appendix Figure 9: The replicated Kaplan–Meier PFS (A) and OS (B) curves of Atezolizumab+bevacizumab (red) and Sunitinib treatments (blue) in IMmotion151 trial. The smooth lines indicated the survival curves predicting their corresponding best survival distributions (The distribution information showed in appendix Table 5). The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI.

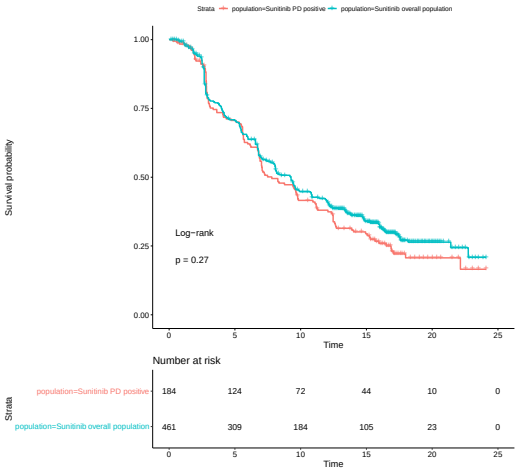


Appendix Figure 10: The replicated Kaplan–Meier PFS (blue) and OS (red) curves of sunitinib treatment by pooling the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials. The smooth lines indicated the survival curves predicting their corresponding best survival distributions (The distribution information showed in appendix Table 5). The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI.

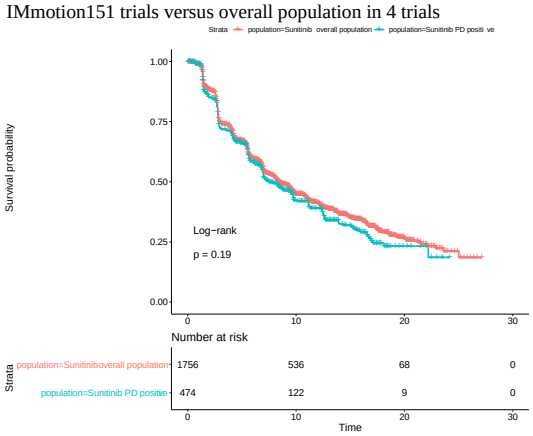
A. PFS in JAVELIN Renal 101 trial



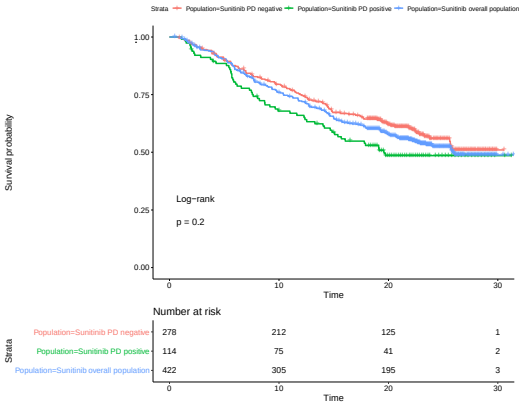
B. PFS in IMmotion151 trial



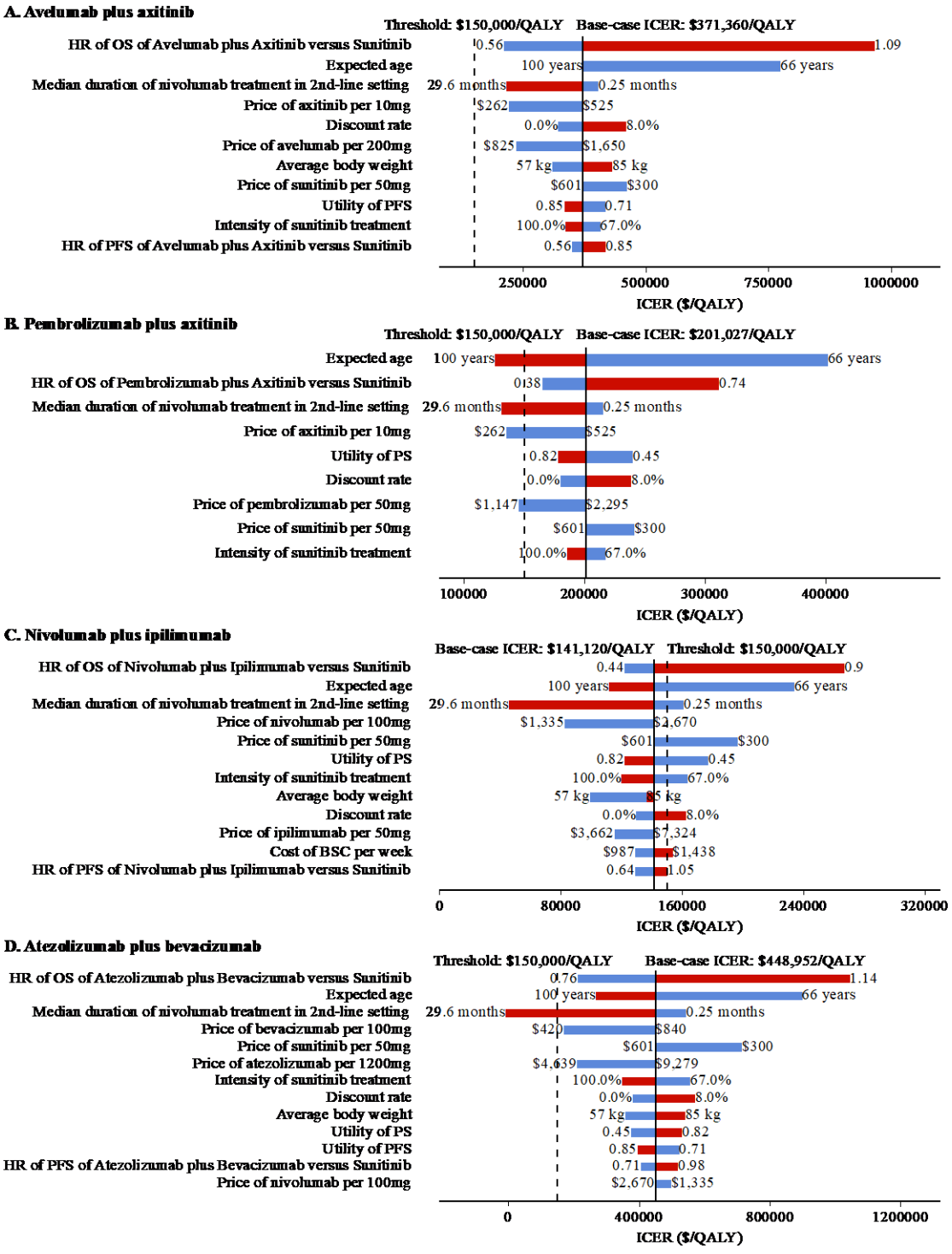
C. PFS in PD-L1–positive tumors from JAVELIN Renal 101 and IMmotion151 trials versus overall population in 4 trials



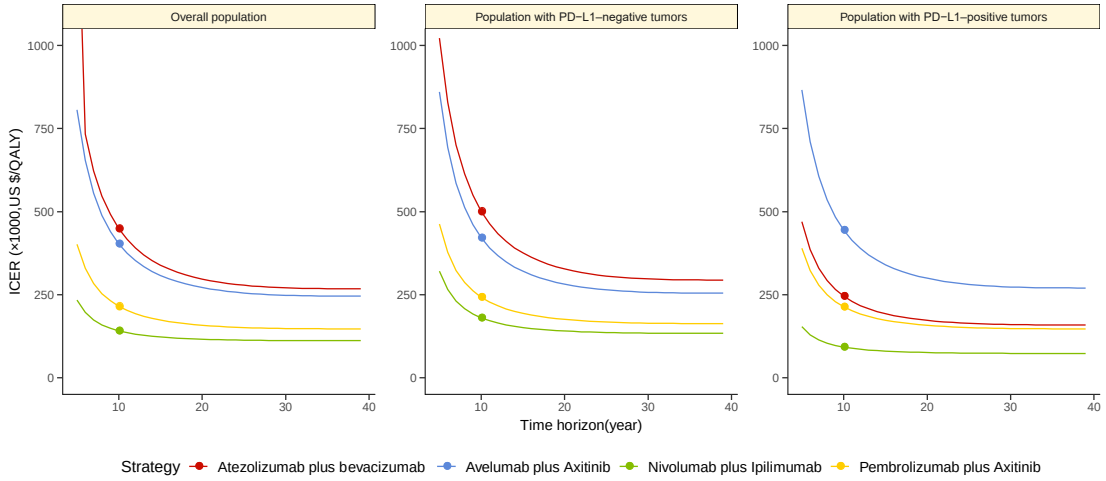
D. OS in CheckMate 214 trial



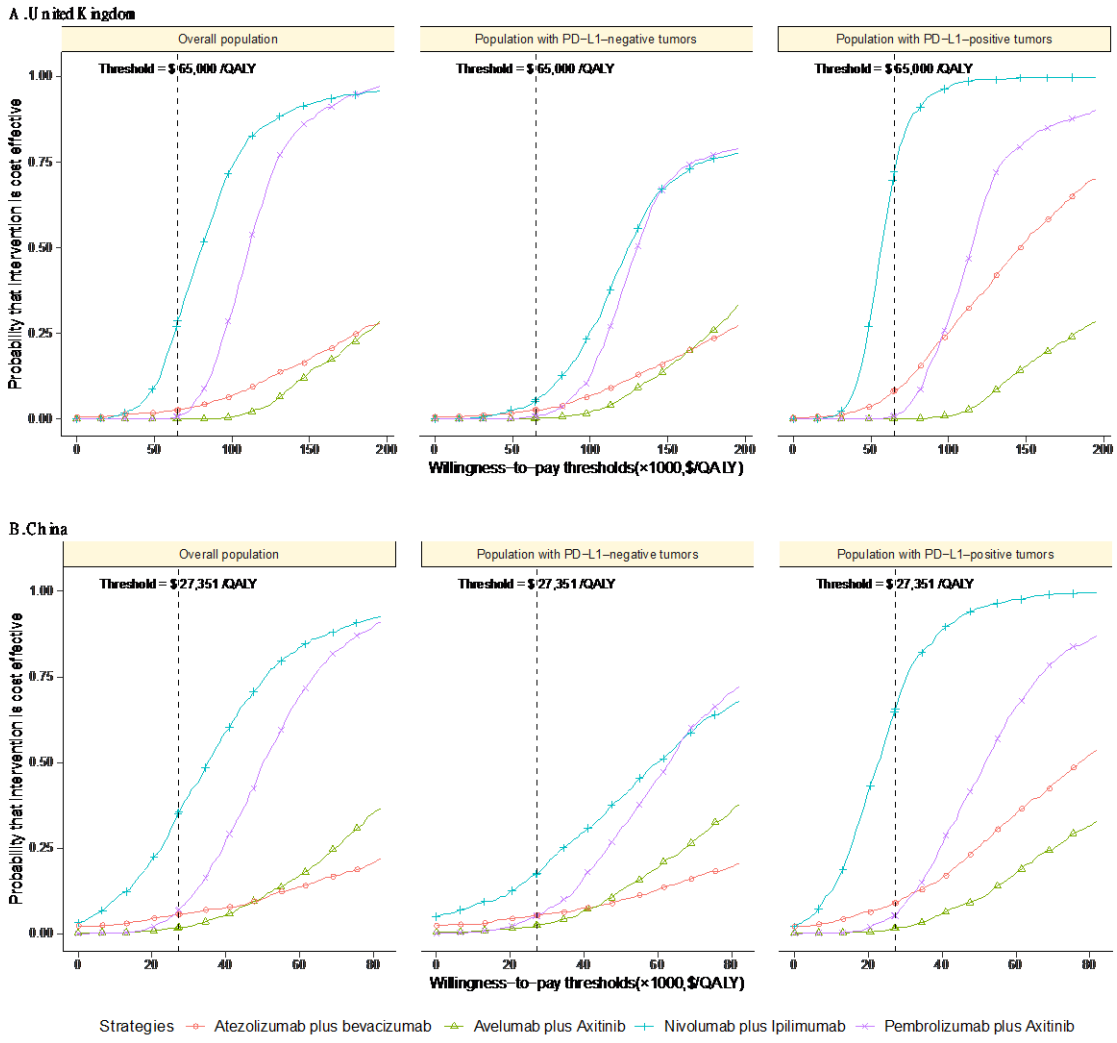
Appendix Figure 11: The replicated PFS of sunitinib treatment in PD-L1–positive tumors versus overall population form the JAVELIN Renal 101 (A), IMmotion 151 trials (B) and the pooled PFS data in PD-L1–positive tumors from JAVELIN Renal 101 and IMmotion 151 trials versus pooled PFS data in overall population from the CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials (C). The replicated OS of sunitinib treatment in PD-L1–positive and negative tumors versus overall population form the CheckMate 214 (D).



Appendix Figure 12: One-way sensitivity analyses of avelumab plus axitinib (A), pembrolizumab plus axitinib (B), nivolumab plus ipilimumab (C) and atezolizumab plus bevacizumab (D) in comparison with sunitinib.



Appendix Figure 13: The impact of time horizon on ICERs. The points indicated the baseline time horizon (10 years) in overall population, PD-L1–positive and negative tumors.



Appendix Figure 14: The cost-effectiveness acceptability curves for avelumab plus axitinib, pembrolizumab plus axitinib, nivolumab plus ipilimumab and atezolizumab plus bevacizumab strategies compared to the sunitinib strategy in overall population, PD-L1–positive and negative tumors in UK (panel A) and China (panel B).

Appendix Table 1: PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	***3***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node*	***Appendix table 3***

		(with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***4***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	4
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	4
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:	4

		• Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Appendix Figure 1
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***Appendix Figure 3***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Not applicable
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix Table 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***5***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	Figure 1and 2
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Not applicable

Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	Figure 1and 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
			7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix table 2: CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1/1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2/1-33
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	3/19-21
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Appendix file 2: 2/19-21
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	3/19-25
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Appendix file 2: 3/23
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Appendix file 2: 2/6-7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why	Appendix file 2: 2/12

		appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Appendix file 2: 2/22
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Appendix file 2: 2/21-23
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Appendix file 2: 2/29-36
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Appendix file 2: 4/2-9
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Appendix file 2: 3/29-44
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Appendix file 2: 3/26-27
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Appendix file 2: 2/5-8; appendix figure 5
Assumptions	16	Describe all structural or other assumptions underpinning	Appendix

		the decision-analytical model.	file 2: 2/15-16; 3/8-9; 3/38; 4/17
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Appendix file 2: 4/11-41
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Appendix Table 5-6
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 1

1

Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	**NA**
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	7/21-30
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	7/6-29
Discussion			
Study findings, limitations, generalizability, and	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the	8/22-25; 9/40-42; 10/2-8

current knowledge		generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	10/20-21
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	10/20-21

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

1

Appendix table 3: Summary of the review inclusion and exclusion criteria

Clinical effectiveness	Inclusion Criteria	Exclusion Criteria
Population	Patients with previously treated advanced or metastatic renal cell carcinoma	Patients <18 years of age
		Healthy subjects
		Animal studies
Intervention	The regimens containing the following ICIs in the first-line setting:	
	Pembrolizumab	
	Nivolumab	Interventions in the second- (and further-) line setting
	Atezolizumab	
	Durvalumab	
	Avelumab	
	Note: Combination therapies also possible	
Comparators	Any, including placebo and best supportive care (BSC)	Radiotherapy, surgery and other non-pharmaceutical treatments
Outcomes	Overall survival	Patient-reported outcomes
	Progression free survival	Biomarker results
	Adverse events	Safety results
Trial Design	Randomised controlled trial (RCT)	Non-RCT
	Systematic reviews, meta-analyses, HTA for screening of bibliographies only	Comments, letters, editorials Non-systematic reviews
Timeframe	All publication years	
Language restrictions	English	Non-English

2

3

Appendix Table 4. Characteristics of randomised controlled trials included in the meta-analysis.

Author	Study name	Year	Study type	Population	Sample size	Intervetion	Control	PFS(month)	ORR	Adverse events	PD-L1 assay	PD-L1 positivity (%)
Rini et al.	KEYNOTE-426	2019	RCT	Advanced Renal-Cell Carcinoma	861	Pembrolizumab+Axitinib	Sunitinib	15.1 VS 11.1	59.3% VS 35.7%	75.8% VS 70.6%	22C3 (Dako)	>1
Motzer et al.	JAVELIN Renal 101	2019	RCT	Advanced Renal-Cell Carcinoma	886	Avelumab+Axitinib	Sunitinib	13.8 VS 8.4	51.4%VS 25.7%	71.2% VS 71.5%	SP-263 (Ventana)	>1
Motzer et al.	Immotion 151	2018	RCT	Advanced Renal-Cell Carcinoma	915	Atezolizumab+Bevacizumab	Sunitinib	11.7 VS 6.1 VS 8.4	32% VS 25% VS 29%	63% VS 40% VS 69%	SP-142 (Ventana)	>1
Motzer et al.	CheckMate 214*	2018	RCT	Advanced Renal-Cell Carcinoma	1096	Nivolumab+Ipilimumab	Sunitinib	11.6 VS 8.4	42% VS 27%	46% VS 63%	28-8 (Dako)	>1

* The data were showed in patients with intermediate and poor risk

1
2
3

Appendix table 5: Parameters of parametric models for virtual time-to-event data,

Trial names	Treatment regimens	Endpoint	Distribution	Distribution information	AIC
CheckMate 214	Sunitinib	PFS	Log-logistic distribution	shape:1.418 (se:0.0755),scale:39.5201 (se:2.6979)	AIC: 2371.48
		OS	Log-logistic distribution	shape:1.3424 (se:0.0857),scale:110.3086 (se:8.3993)	AIC: 2263.86
	Nivolumab+ipilimumab	PFS	Royston-Parmar spline model	gamma0:-7.0412 (se:0.575),gamma1:2.6552 (se:0.2915),gamma2:0.1087 (se:0.0168)	AIC: 2423.88
		OS	Log-normal distribution	meanlog:5.3082 (se:0.1235),sdlog:1.5739 (se:0.1078)	AIC: 1815.59
IMmotion 151	Sunitinib	PFS	Log-logistic distribution	shape:1.5605 (se:0.0742),scale:39.8611 (se:2.1885)	AIC: 3048.4
		OS	Log-logistic distribution	shape:1.1625 (se:0.074),scale:150.6874 (se:13.113)	AIC: 2428.62
	Atezolizumab+bevacizumab	PFS	Royston-Parmar spline model	gamma0:-7.6387 (se:0.6305),gamma1:2.4168 (se:0.2622),gamma2:0.134 (se:0.0256)	AIC: 2873.1
		OS	Gamma distribution	shape:1.1397 (se:0.0968),rate:0.0056 (se:8e-04)	AIC: 2457.61
JAVELIN Renal 101	Sunitinib	PFS	Log-logistic distribution	shape:1.2803 (se:0.0713),scale:35.26 (se:2.6486)	AIC: 2190.07
		OS	Log-logistic distribution	shape:1.2323 (se:0.1256),scale:184.123 (se:30.9467)	AIC: 1007.01
	Avelumab+axitinib	PFS	Royston-Parmar spline model	gamma0:-6.1074 (se:0.5327),gamma1:2.0208 (se:0.2675),gamma2:0.092 (se:0.0218)	AIC: 1942.39
		OS	Exponential	rate:0.0029 (se:4e-04)	AIC:

			distribution		878.04
KEYNOTE-426	Sunitinib	PFS	Log-logistic distribution	shape:1.2474 (se:0.066),scale:35.9047 (se:2.5936)	AIC: 2530.73
		OS	Log-logistic distribution	shape:1.1708 (se:0.1083),scale:168.7267 (se:24.6514)	AIC: 1240.99
	Pembrolizumab+axitinib	PFS	Royston-Parmar spline model	gamma0:-6.122 (se:0.5307),gamma1:2.0243 (se:0.2629),gamma2:0.0928 (se:0.0213)	AIC: 2216.74
		OS	Exponential distribution	rate:0.0024 (se:3e-04)	AIC: 831.95
Pooling data of CheckMate 214, KEYNOTE-426, IMmotion 151 and JAVELIN Renal 101 trials	Sunitinib	PFS	Log-logistic distribution	shape:1.3705 (se:0.0357),scale:37.5566 (se:1.2562)	AIC: 10134.28
		OS	Log-logistic distribution	shape:1.2800 (se:0.05),scale:135.14 (se:7.02)	AIC: 6398.76

Abbreviations: AIC, Akaike information criterion.

Appendix Table 6. Cost (US $) estimates (expected value [range]).

Parameters	United Kingdom	China
Price of sunitinib per 50 mg	145.7 (72.87 - 145.7) [# 24]	66 (33 - 66) [#&]
Price of ipilimumab per 50 mg	4,875 (2,438 – 4,875) [#15]	4,655 (2328 - 7324)* [#]
Price of nivolumab per 100 mg	1,426 (713.1 – 1,426) [# 15]	1362 (680.9 - 1362) [#&]
Price of avelumab per 200mg	998 (499 - 998) [#37]	953 (477 - 953) *
Price of pembrolizumab per 50mg	6,838 (5,498 – 8,178) [#38]	2,635 (1,318 – 2,635) [#&]
Price of axitinib per 10mg	163 (82 - 163) [#25]	61 (30 - 61) [#&]
Price of atezolizumab per 1200mg	4,950 (2,475 – 4,950) [#39]	3,141 (1,570 – 3,141) *
Price of bevacizumab per 100mg	300 (150 - 300) [#40]	284 (142 - 284) [#&]
Cost of follow-up and monitoring per cycle	75.78 (48.32 - 103.2) [24]	6.13 (4.9 - 8.58) [26]
Cost of second-line active treatment per patient	15,012 (14,793 – 15,231) [24]	21,081 (11,927 – 26,628) [26]
Cost of BSC per cycle	88.23 (70.53 - 105.9) [24]	52.53 (49.1 - 69.21) [30]
Cost of terminal care per patient	10,366 (8,566 – 12,849) [19]	1,893 (1564 - 2346) [41]
Cost of managing AEs (grade⩾3) per event		
Fatigue	483.6 (0 - 967.2) [29]	110.3 (82.72 - 137.9) [26]
Hypertension	27.3 (0 - 54.6) [29]	12.35 (9.26 - 15.44) [26]
Anemia	3,242 (3,097 – 3,388) [29]	508.2 (381.2 - 635.3) [26]
Palmar–plantar erythrodysesthesia	131.3 (98.48 - 164.1) [25]	15.21 (8.85 - 21.57) [31]
Thrombocytopenia	4,927 (4,764 – 5,091) [29]	3,395 (2,546 – 4,244) [26]
Cost of drug administration per unit	405.3 (304 - 506.7) [15]	17.65 (13.24 - 22.06) [26]

* The prices were assumed by multiplying the price of ipilimumab in UK and the ratio of the price of nivolumab between UK and China.

&Local hospital charge.

The ranges were assumed for sensitivity analysis.

Appendix Table 7. Summary of base-case cost ($) and outcome results from the perspective of the National Health Service in UK.

Strategy	Cost	Overall LYs	QALYs	ICER*
Overall population				
Sunitinib	63,855	4.03	2.55	NA
Avelumab plus Axitinib	180,450	4.80	3.07	223,841
Pembrolizumab plus Axitinib	190,046	5.96	3.71	108,825
Nivolumab plus Ipilimumab	137,999	5.46	3.40	87,803
Atezolizumab plus bevacizumab	122,316	4.26	2.73	330,607
Population with PD-L1–positive tumors				
Sunitinib	62,266	3.48	2.24	NA
Avelumab plus Axitinib	186,684	4.08	2.71	267,240
Pembrolizumab plus Axitinib	195,755	5.37	3.42	113,459
Nivolumab plus Ipilimumab	158,249	5.90	3.82	60,866
Atezolizumab plus bevacizumab	125,249	4.00	2.62	166,562
Population with PD-L1–negative tumors				
Sunitinib	64,786	4.37	2.74	NA
Avelumab plus Axitinib	171,042	5.14	3.22	222,114
Pembrolizumab plus Axitinib	173,547	5.96	3.65	119,124
Nivolumab plus Ipilimumab	130,138	5.34	3.29	119,608
Atezolizumab plus bevacizumab	120,948	4.59	2.90	350,504

*Incremental cost per QALY (versus sunitinib strategy)

Appendix Table 8. Summary of base-case cost ($) and outcome results from the perspective of Chinese health care perspectives.

Strategy	Cost	Overall LYs	QALYs	ICER*
Overall population				
Sunitinib	33,640	4.03	2.46	NA
Avelumab plus Axitinib	77,386	4.80	2.95	89,643
Pembrolizumab plus Axitinib	88,562	5.96	3.54	50,742
Nivolumab plus Ipilimumab	63,395	5.46	3.25	37,701
Atezolizumab plus bevacizumab	62,987	4.26	2.62	176,050
Population with PD-L1–positive tumors				
Sunitinib	32,551	3.48	2.16	NA
Avelumab plus Axitinib	78,586	4.08	2.60	105,165
Pembrolizumab plus Axitinib	89,979	5.37	3.27	52,158
Nivolumab plus Ipilimumab	67,570	5.90	3.64	23,740
Atezolizumab plus bevacizumab	63,736	4.00	2.52	87,586
Population with PD-L1–negative tumors				
Sunitinib	34,289	4.37	2.63	NA
Avelumab plus Axitinib	74,637	5.14	3.08	90,225
Pembrolizumab plus Axitinib	82,518	5.96	3.48	56,674
Nivolumab plus Ipilimumab	61,298	5.34	3.14	52,959
Atezolizumab plus bevacizumab	62,811	4.59	2.78	189,232

*Incremental cost per QALY (versus sunitinib strategy)

Appendix Table 9. Summary of Cost ($) and Outcome Results at first three months.

Strategy	Cost	Overall LYs
Overall population		
Sunitinib	10744	0.2445
Avelumab plus Axitinib	37652	0.2455
Pembrolizumab plus Axitinib	41815	0.2468
Nivolumab plus Ipilimumab	52198	0.2463
Atezolizumab plus bevacizumab	39281	0.2448
Population with PD-L1–positive tumors		
Sunitinib	10832	0.2435
Avelumab plus Axitinib	37883	0.2445
Pembrolizumab plus Axitinib	42007	0.2462
Nivolumab plus Ipilimumab	53019	0.2467
Atezolizumab plus bevacizumab	39490	0.2444
Population with PD-L1–negative tumors		
Sunitinib	10699	0.245
Avelumab plus Axitinib	37421	0.246
Pembrolizumab plus Axitinib	41461	0.2468
Nivolumab plus Ipilimumab	51790	0.2462
Atezolizumab plus bevacizumab	39124	0.2453

*Incremental cost per QALY (versus sunitinib strategy)