Treatments for renal cell carcinoma [ID6186]: A Pathways Pilot Appraisal

Preliminary Assessment Report

Produced by

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Acronym	Definition
AE	Adverse event
AG	Assessment group
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BMJ	British Medical Journal
BMS	Bristol Myers Squibb
BNF	British National Formulary
BRL	Brazilian Real
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CPI	Consumer Price Index
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
DBL	Database lock
DES	Discrete event simulation
DF	Degrees of freedom
DIC	Deviance information criterion
DICE	Discretely integrated condition event
DM	Distance metastases
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EMA	European Medicines Agency
ERG	External review group

Acronym	Definition
ESMO	European Society for Medical Oncology
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index - Disease Related Symptoms
FP	Fractional polynomials
GBP	Great British Pounds
GP	General practitioner
GU	Genito urinary
HES	Hospital Episode Statistics
HRG	Health resource group
HRQoL	Health-related quality of life
HSE	Health Survey England
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
ICTRP	International Clinical Trials Registry Platform
IMDC	International Metastatic RCC Database Consortium
INAHTA	International Network of Agencies for Health Technology Assessment
IO	Immuno-oncology
IPD	Individual patient data
IV	Intravenous
IVI	Innovation and Value Initiative
KM	Kaplan Meier
KPS	Karnofsky performance status
LDH	Lactate dehydrogenase
LR	Local recurrence
LYG	Life years gained
MA	Meta-analyses
MCM	Mixture-cure model
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MRU	Medical resource use
MSKCC	Memorial Sloan Kettering Cancer Center
MTA	Multiple technology appraisal
NB	Net benefit
NCRAS	National Cancer Registration and Analysis Service

Acronym	Definition
NEJM	New England Journal of Medicine
NHS	National Health Service
NHSE	National Health Service, England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PD	Progressive disease
PF	Progression free
PFS	Progression-free survival
PICOS	Population, Intervention, Comparison, Outcomes and Study
PLD	Patient level data
PPS	Post progression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dosing intensity
RWD	Real-world data
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Therapy
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
STA	Single technology appraisal
TA	Technology appraisal

Acronym	Definition
TE	Treatment effect
TKI	Tyrosine kinase inhibitor
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
TTP	Time to progression
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization
ZIN	Zorginstituut Nederland National Health Care Institute

1. PLAIN LANGUAGE SUMMARY

There are many drug treatments currently available for renal cell carcinoma, or RCC, which is a type of cancer that begins in the kidney. NICE have requested that the EAG develop a model which incorporates the entire treatment pathway of a disease, to reduce duplication of work and allow consideration of the pathway of treatments This will not include any surgeries for RCC, any drug treatments that are given in combination with or immediately following surgery, nor any non-drug treatments. This project will then use the treatment pathway model which has been developed to evaluate a new drug combination (cabozantinib and nivolumab) as a first treatment option for people with a form of RCC that has spread to other areas of the body.

We are currently part-way through this project. So far, we have sought evidence for how effective treatments are for people with advanced RCC. We identified 30 trials of treatments that had been published, which gave us information about how effective treatments are (e.g. for slowing cancer progression) and what side effects they had. Of these, 1 trial was evaluating the new treatment of cabozantinib and nivolumab and 29 trials were evaluating treatments already available in the NHS. The company who makes cabozantinib will be sending us additional data about how well this combined treatment works. We are currently preparing a large statistical analysis that we will use to compare the treatments against each other and tell us which are best for different groups of people with RCC. This includes which treatment is best depending on how aggressive someone's cancer is.

We have also begun to build a mathematical model (called a decision model) to simulate the current clinical practice in England and Wales and their clinical and economic outcomes for people with RCC and the NHS. This will include consideration of drug and administration costs, the costs of managing the disease, and the impact of different treatments on treatment effectiveness and quality of life for people with different stages of RCC.

We have identified 15 potentially relevant data sources containing real life information about people with RCC, including information about them such as their age, how aggressive their cancer is, how RCC has impacted their quality of life, and what treatments they received. We will include this information in the decision model

alongside information about all of the treatments, including what our statistical analyses tell us about how effective they are in comparison. We will also incorporate other types of information, including how much each of the treatments costs the NHS and which NHS staff and services are needed to treat people with RCC. Where we cannot find data for information we need, we will ask the opinions of a group of experienced NHS clinicians.

Our decision model of RCC in the NHS will allow NICE to explore many things, including whether sufficient data exists to determine in which order treatments should be given to people with RCC and which treatments offer the best value for people with RCC and the NHS. The rationale for this is that using different treatments could result in different subsequent treatment regimens being available and / or different outcomes for patients.

Initially, the Committee will use the decision model to decide whether the new combination, cabozantinib plus nivolumab, should be one of the options used to treat people with RCC in the NHS. Exploratory subsequent analyses may then be conducted. These will only consider treatments within their recommendations and where there are multiple options at the same point in the treatment pathway. After this project ends, NICE will be able to keep the decision model up to date with new evidence and use it to help decide on new treatments for RCC to help ensure that there is consistency in evaluating treatments in the same disease area.

At the time of writing, we are partway through the project, but we are still waiting to receive evidence from the company about how effective cabozantinib plus nivolumab is for people with RCC. Once we receive this, we will conduct our statistical analyses and finish building the decision model. This document explains all the work that we've completed so far and describes the methods that will be used in the next steps of the project.

2. OBJECTIVES OF THE PILOT PROCESS AND THIS ASSESSMENT

The NICE Pathways pilot process aims to capitalise on the efficiencies of assessing multiple technologies in a disease pathway and inform robust access decisions by building an evolving core model for a disease area.

NICE selected RCC as the first pilot topic because of the expected pipeline of treatments. Additionally, RCC is a disease area that incorporates multi-comparator decision spaces, with dynamic decision making based on exposure to prior therapies, providing potential to effectively pilot and learn from the pathways process.

As part of this pilot NICE have requested that the EAG develop a model which incorporates multiple decision nodes in order to assess multiple technologies in a disease pathway and inform robust access decisions. NICE have published a process statement outlining the summary of this pilot and the intended process to achieve its aims (a reference to this will be included when available).

Within this pilot we aim to develop a high-quality open-source disease model, available to all relevant stakeholders without restriction, which can be reused and built upon in future appraisals whilst maintaining confidentiality of proprietary data.

An attractive model for this type of approach is the Innovation and Value Initiative's Open-Source Value Project (IVI; Jansen et al. 2019[1]). Since the project began in 2018, IVI has developed three disease models – one in rheumatoid arthritis, one in non-small-cell lung cancer and one in major depressive disorder – that are made freely available to all users, with full open-source code posted in a public repository (GitHub). [2] As part of their development process, IVI holds regular public consultation seeking feedback on the structure and parameterisation of its analyses, and exposing their implementation to unrestricted scrutiny.

Given the scope and steps of the process the consultation stage is different to the IVI models. In particular a user-interface will not be provided prior to the Appraisal Committee meeting and is scheduled instead for a later phase of work (see Section 5.3.1.7). However, the code will be posted in a public repository enabling full public scrutiny and as discussed additional functionality will be incorporated during Phase 2 of the pilot.

2.1. Contents of this report

This report provides a summary of work undertaken by the EAG prior to the receipt of data from manufacturers, observational patient datasets and formal input from clinical experts. All

information reported herein is from publicly available datasets and focuses on detailing the EAG's current understanding of the health condition, treatment pathway, decision problem for the initial appraisal, evidence base and therefore expected economic analysis inputs and methods. At the time of submission, the EAG had finalised the methods that will be used in its evaluation, identified all the relevant published evidence, identified real-world evidence (RWE) sources, developed an analysis plan, and developed a number of modules for the decision model and a draft of the Excel input sheet. This report does not contain any results as these will be provided in the final report.

3. DECISION PROBLEM, DESCRIPTION OF THE TECHNOLOGIES AND CLINICAL CARE PATHWAY

3.1. Description of the health condition

RCC is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer, accounting for more than 80% of cases. [3] There are several types of RCC. The main ones are clear cell (accounting for around 75% of cases), papillary and chromophobe. [3]

Treatment depends on the location and stage of the cancer. [4] There are different staging systems for RCC, including the number system that looks at the number and size of kidney tumours. The number system has four stages:

- Stage 1 and 2 (early stage where the tumour is localised to the kidney)
- Stage 3 (locally advanced stage with possible spread to regional lymph nodes)
- Stage 4 (advanced, metastatic stage where the tumour has spread beyond regional lymph nodes to other parts of the body).

The scope for this appraisal is for people with advanced or metastatic RCC. Although systemic treatments are mostly suitable for those with metastatic disease (Stage 4), they may be offered to people with locally advanced (Stage 3) disease where this is unresectable. Due to this, people with Stage 4 RCC or Stage 3 unresectable RCC have been included in this appraisal.

3.2. Epidemiology

Kidney cancer is the seventh most common cancer in the UK, accounting for 4% of all new cancer cases (2016-2018). [5] Kidney cancer is more common in men than in women: in the UK, between 2016 and 2018, there were 1.7 times more new cases in men than in women. A quarter of cases were diagnosed in people aged 60 to 69 years, with nearly half of cases (49.7%) diagnosed in people aged ≥70 years. [5]

In 2018, 9,438 new kidney cancer cases were diagnosed in England. [6] Of those, 40.2% had stage 1 disease, 7.6% had stage 2 disease, 15.5% had stage 3 disease and 20.5% had stage 4 disease. [4] The 5-year survival was 86.8%, 76.6%, 74.2% and 12.4% for stage 1, 2, 3, and

stage 4 disease, respectively.[7] These survival rates are likely to underestimate survival for patients starting treatment now as they do not include the impact of immuno-oncology combinations that have more recently entered clinical practice.

Overall survival data were available from the Get Data Out (GDO) 'Kidney' dataset, published by the NCRAS. Yearly data (from 2013 to 2019) were recorded for stage 1, 2, 3 and 4 clear cell RCC patients, and for renal cell carcinoma not otherwise specified (NOS) patients where diagnosis has been histologically confirmed and not histologically confirmed. Survival rates were reported as Kaplan-Meier (KM) estimates at month, 3, 6, 9, 12, 24, 36, 48, 60, 72 and 84. The most complete data were for 12 months i.e. 12 month data were reported for all years.

The data indicate that patients with stage 3 clear cell RCC have the best 12-month prognosis/ highest survival rates (ranging from 93.9% to 95%). The majority of these patients will not be eligible for surgery and therefore not in scope of this appraisal.

For stage 4 clear cell RCC, which is the histology in which the majority of clinical trials have been conducted and is the most common, 12-month survival ranged from 58.5% to 62.2% (Figure 1 and Figure 2). The most severe histological subtype with the lowest 12-month overall survival estimates were patients with stage 4 renal cell carcinoma NOS (not histologically confirmed), ranging from 13.1% to 18.4%.

The data suggest that there has been a sustained improvement in overall survival from 2016 to 2019 for patients with stage 4 renal cell carcinoma NOS (histologically confirmed), with overall survival increasing from 28.5% to 38%. Although the cause for improved survival rates is not clear, it may be due to patient enrolment in clinical trials focussing on non-clear cell histologies.

Figure 1: 12-month overall survival for stage 3 and 4 clear cell RCC (2013-2019)

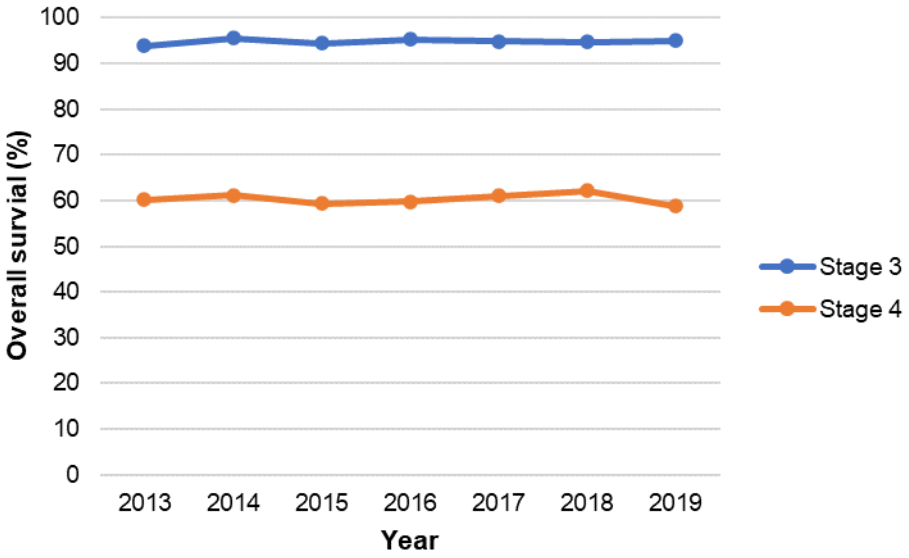
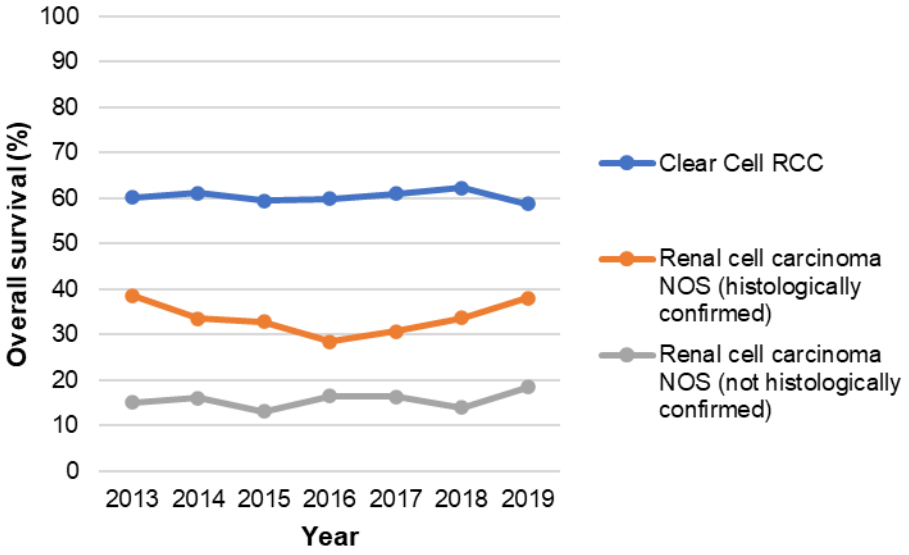


Figure 2: 12-month overall survival for stage 4 cancer, all histologies (2013-2019)



Five-year (60 month) survival rates were recorded for years 2013, 2014 and 2015. For completeness and for validation purposes these are outlined below. OS at 60 months confirm that patients with stage 3 clear cell RCC have the best 12-month prognosis/ highest survival rates (ranging from 70.8% to 72.4%). For stage 4 clear cell RCC, 60-month survival ranged

from 19.1% to 20.1%. Patients with stage 4 renal cell carcinoma NOS (not histologically confirmed) have the poorest 12-month prognosis/lowest survival rates (ranging from 2.1% to 2.7%).

Figure 3 and Figure 4 show that the prognosis for clear cell RCC remained relatively consistent between 2013 and 2019, however, as noted earlier these survival rates are likely to underestimate survival for patients starting treatment now as they do not include the impact of immuno-oncology combinations that have more recently entered clinical practice for which any improvements are most likely to be seen in longer term data.

Figure 3: Overall survival for patients with stage 3 clear cell RCC (all years)

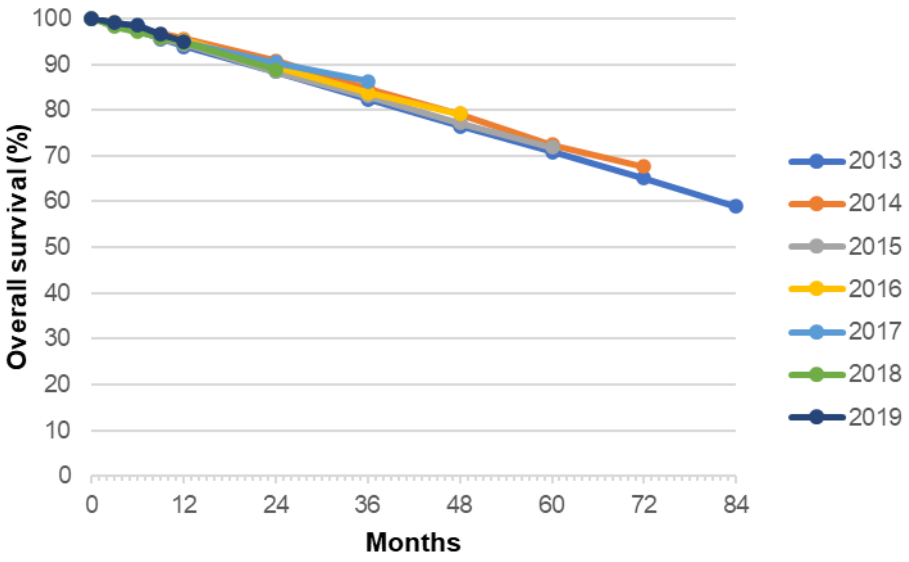
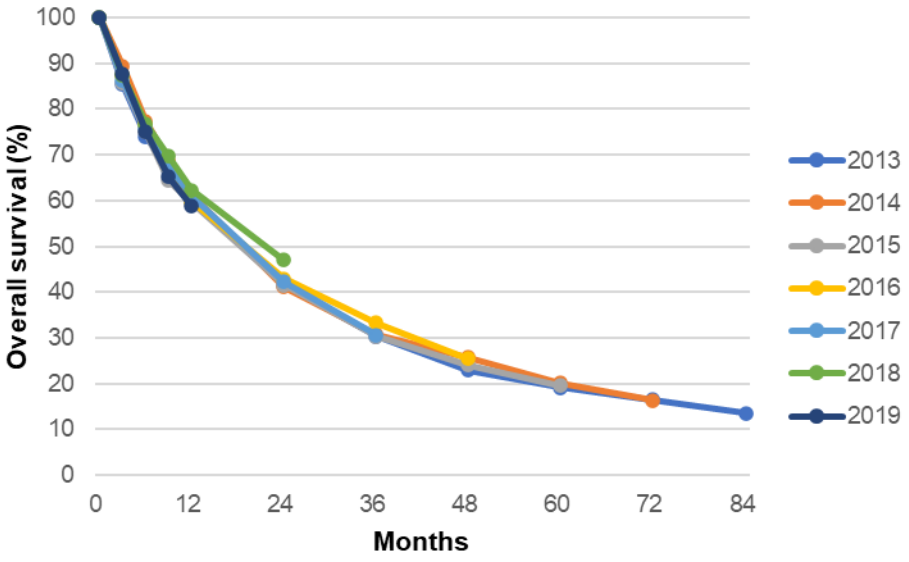


Figure 4: Overall survival for patients with stage 4 clear cell RCC (all years)



3.3. Risk status

Risk status for patients with advanced RCC who have not received systemic therapy is classified using the International Metastatic RCC Database Consortium (IMDC) risk score. [8,9] This scoring system was derived from a population of patients with metastatic RCC treated with VEGF-targeted therapy and predicts survival based on time from diagnosis, Karnofsky performance status, and laboratory measures of haemoglobin, corrected calcium and neutrophils. Within the current treatment pathway for RCC, some treatments are only recommended for people with IMDC poor or intermediate risk status (Section 3.4). The relevance of IMDC prognostic criteria to frontline combination immunotherapy remains to be fully established, however, these criteria are still used to risk-stratify patients enrolled into clinical trials and determine available treatment options in practice. [10]

Historically, risk status was classified using another risk stratification model: the Memorial Sloan Kettering Cancer Center (MSKCC) model. [11,12] The MSKCC model was extended to create the IMDC system so as to increase sensitivity for predicting survival outcomes, and is now the measure most commonly used in UK practice. The differences between the two are that the MSKCC model includes lactate dehydrogenase concentration, and the IMDC model considers absolute neutrophil count and platelet count which are not included in the MSKCC model. In a study to validate the IMDC, Heng et al 2013 reported that 83% of patients were classified into the same risk subgroup by both models. [9] A more recent study found that by Okita et al found that disagreements were mostly on whether patients should be classified as either intermediate or poor risk. [13] For the purposes of this appraisal, these differences are likely to be of limited impact as these groups are generally pooled within NICE recommendations.

The majority of people treated in UK practice have intermediate or poor risk status. A chart review of 652 people treated at first-line in two large UK hospitals between January 2008 and December 2015 reported that 89% of people for whom MSKCC risk was recorded had intermediate or poor risk status. [14] In the observational ADONIS study in Europe, 69% of 238 participants receiving sunitinib first-line between October 2014 and May 2018 had IMDC intermediate or poor risk status. [15]

The international study validating the IMDC score reported by Gore et al. in 2015 reported a median OS of 45.5 months for favourable risk, 18.9 months for intermediate risk and 6.2 months for poor risk using data from 4,065 participants between 2004 and 2010. [16] A 2017 abstract investigating real-world outcomes of 255 people treated with immuno-oncology agents

by IMDC status by Yip et al. found that whilst survival data were too immature to evaluate at first-line, IMDC risk status was predictive at second-line with median OS rates not reached, 26.7 months, and 12.1 months ($p<0.0001$) in each of the three risk groups. [17]

3.4. Treatment pathway

The treatment pathway for RCC can be divided into interconnected decision points based on the disease staging system and line of therapy (see Figure 5 and Figure 6). The treatment pathway is based upon people with clear cell histology (as are the majority of trials; Section 4.2.2.2). In practice, the same treatment algorithm is applied to the majority of people with non-clear cell histologies including papillary RCC, chromophobe RCC, collecting duct RCC (Bellini collecting duct RCC), medullary RCC - mucinous tubular and spindle cell RCC, multilocular cystic RCC, XP11 translocation RCC and unclassified RCC. [18] Information on the specific histologies where treatments are commissioned in the same manner as clear-cell has been requested from NHSE and will be incorporated into the project findings when received.

3.4.1. Treatment for early stage to locally advanced RCC

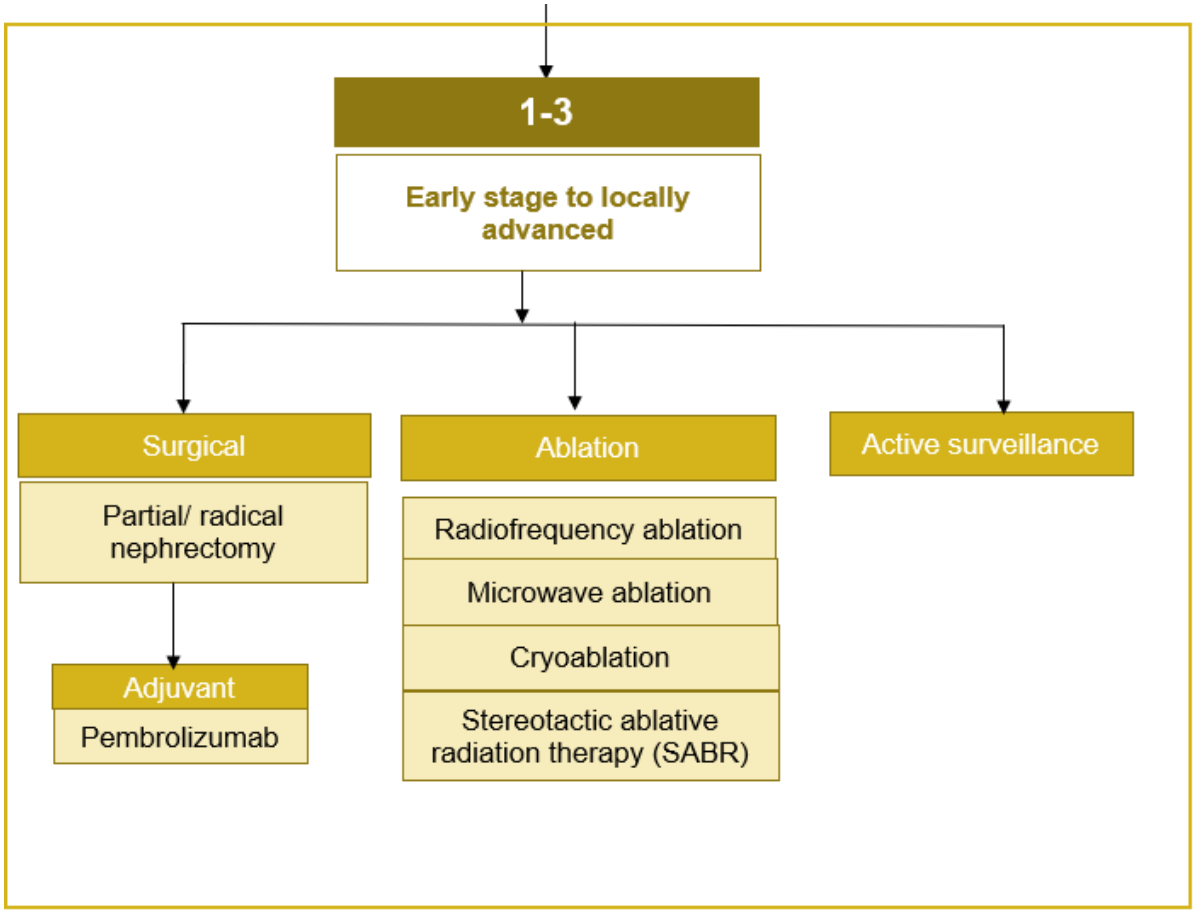
Surgery (partial or radical nephrectomy) is usually possible, and is the preferred treatment, for people with early stage to locally advanced RCC and is usually curative. [19] Approximately 20 - 40% of people who have received surgery subsequently develop metastatic RCC. [20]

NICE recommended pembrolizumab as an option for the adjuvant treatment of RCC at increased risk of recurrence after nephrectomy, with or without metastatic lesion resection in October 2022. [21] Receipt of pembrolizumab in the adjuvant setting may restrict later treatment options. The reason for this being that the NHS does not fund treatment with subsequent immuno-oncology treatments for people who have received treatment with a PD-1/PD-L1 inhibitor in the adjuvant setting in the previous 12 months.

Local ablation is an alternative first-line approach of particular use in people whose renal function needs to be preserved. [22] The most commonly utilised of these techniques are radiofrequency ablation and cryoablation. [22]

Active surveillance may also be appropriate for early stage RCC, particularly where the mass is small and/or in those who are elderly or frail. [22]

Figure 5: Treatment pathway for early stage to locally advanced RCC



3.4.2. Treatment for advanced RCC

In selected individuals with IMDC favourable risk disease and low tumour burden the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) clinical practice guidelines suggest that active surveillance may be an appropriate option, [23,24]. However, the BMJ RCC best practice guidelines (July, 2022) guidelines do not include active surveillance in the treatment algorithm for advanced RCC . [22] Surgery is only recommended in people where there is a metastasis in a single regional lymph node, but no evidence of distant metastasis. [22] The potential benefits and risks of deferred surgery for residual primary tumours or metastases after partial response to checkpoint inhibitor treatment is, however, gaining interest, considering the potential for long-lasting effects with these treatments. [25]

The optimal approach for people with metastatic disease with a good-to-intermediate prognosis is, however, still being debated. [25]

For people who cannot tolerate or do not wish to receive active treatment, best supportive care (BSC) is provided, which includes the monitoring of progression, symptom control and palliative care without active treatment. [26]

3.4.2.1. Untreated advanced RCC

Current treatment options for untreated advanced RCC include:

- Immunotherapy combination therapy:
    - For people with IMDC intermediate- or poor-risk disease, NICE recommends nivolumab plus ipilimumab (a PD-1 inhibitor with a CTLA-4 inhibitor; TA780) and pembrolizumab plus lenvatinib in patients who would otherwise be suitable for treatment with nivolumab plus ipilimumab (a tyrosine kinase inhibitor [TKI] with a PD-1/PD-L1 inhibitor; TA858)
    - For the broader, all-risk population, avelumab plus axitinib is available via the Cancer Drugs Fund (a PD-1/PD-L1 inhibitor with a TKI, TA645)
- TKI monotherapy: sunitinib, pazopanib or tivozanib as recommended by NICE technology appraisal guidance (TA169, TA215 and TA512) and cabozantinib (TA542 which is only recommended for people with intermediate or poor-risk cancer)

The British Medical Journal (BMJ) RCC best practice guidelines (July, 2022) recommend a similar approach to NICE, though with some variation. [22] Preferred treatment options were either pembrolizumab plus axitinib (not recommended by NICE), cabozantinib plus nivolumab (under evaluation within this analysis), pembrolizumab plus lenvatinib, or nivolumab plus ipilimumab. Secondary options included avelumab plus axitinib, and sunitinib, pazopanib and cabozantinib. Avelumab plus axitinib was considered secondary treatment on the basis that a benefit for OS compared to other treatments had not been demonstrated. [27] TKI monotherapies were considered to be the preferred option for patients who cannot receive or tolerate immune checkpoint inhibition, while tivozanib was considered a tertiary option.

The ESMO guideline recommendations (2021) align with those specified by the BMJ with the exception that monotherapy TKIs sunitinib or pazopanib were considered potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease. [23]

This was due to a lack of clear superiority for PD-1-based combinations over sunitinib in this population.

3.4.2.2. Previously treated advanced RCC

As the approach to treatment of metastatic RCC has changed with the approval of immune checkpoint inhibitors as first-line therapy, there is considerable uncertainty surrounding the optimum treatment pathway for previously treated RCC, and there are limited data on the efficacy of subsequent therapies following the use of immune checkpoint inhibitors. [22]

Current treatment options include:

- Axitinib (following either a cytokine or tyrosine kinase inhibitor; TA333); cytokine inhibitors are not recommended by NICE. Clinical expert input has indicated that tivozanib and axitinib have a similar mechanism of action so would not be used in sequence
- Cabozantinib (following a VEGF-targeted therapy; TA463)
- Lenvatinib plus everolimus (following one prior VEGF-targeted therapy for people with ECOG 0-1; TA498)
- Nivolumab (for people who have only had one or two prior lines of therapy[18] and have not previously had a PD-1/PD-L1 inhibitor; TA417)
- Everolimus (following a VEGF-targeted therapy TA432; this is understood to be used primarily at fourth line)
- A first line TKI (sunitinib, pazopanib or tivozanib) following nivolumab plus ipilimumab

ESMO guideline recommendations are to give a VEGFR that has not previously been given. They note[23] (p.1512 – 1514):

Robust prospective second-line data exclusively after first-line PD-1 inhibitor-based combination therapy are lacking. Prospective datasets exist for axitinib, pazopanib and sunitinib, but they include mixed patient populations and small numbers. There are also retrospective, exploratory, subset analyses … Responses were seen (~20%) in all of these studies and outcome was in line with the expectations for sequencing therapy … It is likely that sequencing different targeted therapies approved in advanced RCC is beneficial, as was

the case in the pre-ICI era. Rechallenge with ICIs is unproven, and should not be regarded as a standard option.

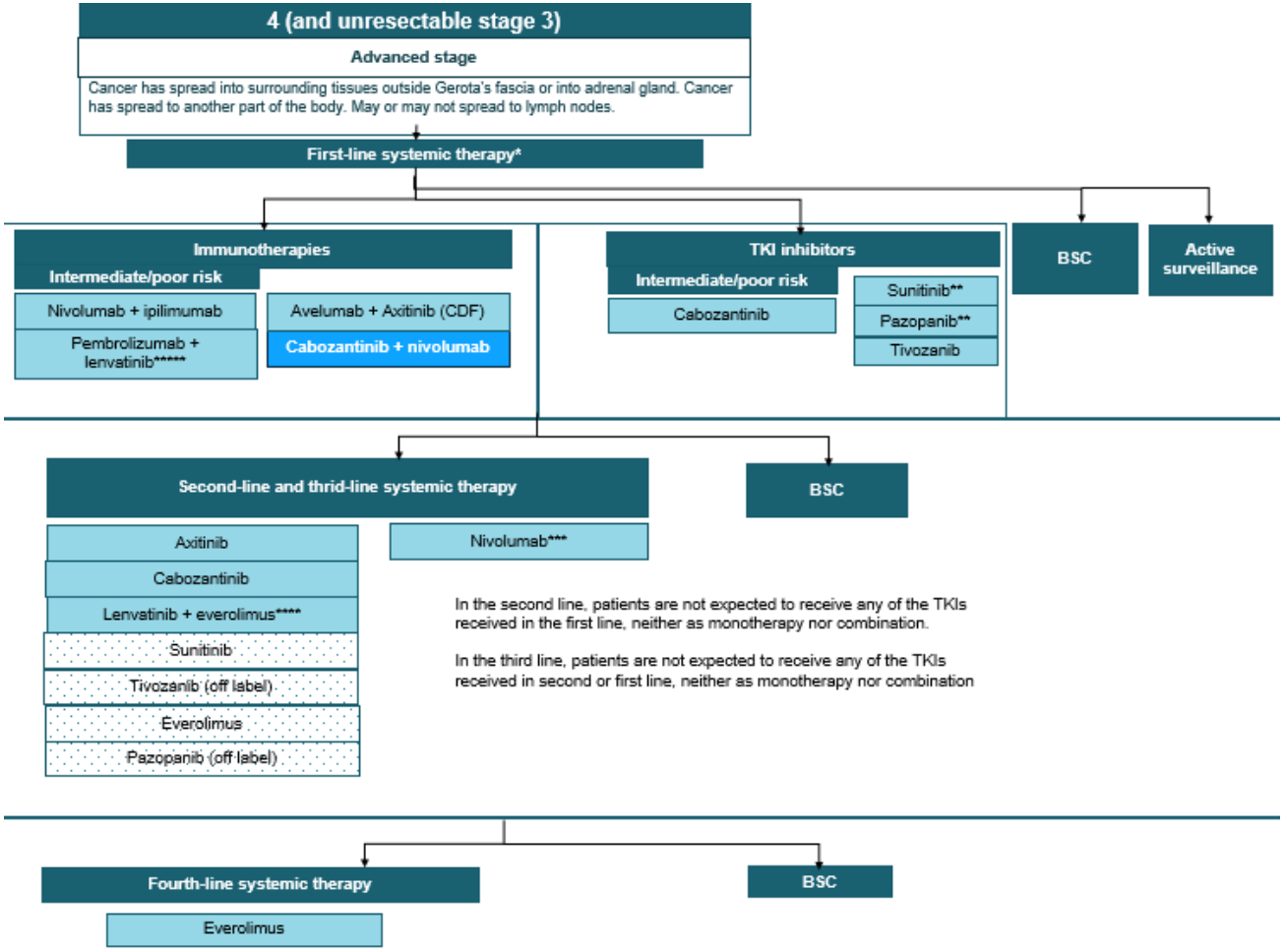
While the BMJ recommendations for previously treated RCC include options not currently recommended in the UK (e.g., aldesleukin, bevacizumab plus interferon alfa, temsirolimus and sorafenib), their broad recommendations are consistent with the ESMO guidelines.

In England some additional recommendations are provided in the Cancer Drugs Fund list: [18]

- Following avelumab and axitinib: either the currently commissioned 2nd line options of cabozantinib or lenvatinib plus everolimus or everolimus monotherapy or the currently commissioned 1st line options of sunitinib (still on label as 2nd line treatment) or pazopanib (off label as 2nd line treatment, or tivozanib (off-label as 2nd line treatment)
- Following pembrolizumab and lenvatinib: either the currently commissioned 2nd line options of cabozantinib or axitinib or everolimus monotherapy or the currently commissioned 1st line options of sunitinib (still on label as 2nd line treatment) or pazopanib (off label as 2nd line treatment) or tivozanib (off label as 2nd line treatment)
- Following nivolumab plus ipilimumab: cabozantinib or pazopanib or tivozanib or sunitinib

These demonstrate that 1st line TKIs are recommended and available in the 2nd line setting in the NHS, with two of these being used off-label, as shown in Figure 6.

Figure 6: Treatment pathway for advanced stage RCC



Notes: * People can only receive treatment with a PD1 / PD-L1 inhibitor if they have not received a prior PD1 / PD-L1 inhibitor in the advanced setting and have not received a prior PD1 / PD-L1 inhibitor within the last 12 months in the adjuvant / neo-adjuvant setting

** Considered potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease (ESMO guideline recommendations; 2021)

*** Nivolumab can only be used if the person has only had one or two prior lines of treatment and has not been previously treated with a mAb either in the advanced setting or less than 12 months prior in the adjuvant / neo-adjuvant setting

**** Lenvatinib + everolimus is only licensed for use after one prior anti-VEGF

***** Pembrolizumab + lenvatinib is only recommended in patients who would otherwise be suitable for treatment with nivolumab plus ipilimumab

3.5. Decision problem

As noted in Section 1, this pilot is designed to address a broader decision problem than is considered within a standard STA. The platform model to be developed will encompass all stages of the treatment pathway for RCC, including all treatments within the treatment pathway for first- and subsequent line systemic treatment (Section 3.4). Within the pilot, the EAG will specifically appraise the clinical and cost effectiveness of one treatment: cabozantinib plus nivolumab for untreated advanced or metastatic RCC. A summary of the decision problem for the appraisal of this treatment is provided in Table 1.

Table 1: Summary of decision problem for the cabozantinib plus nivolumab

	Final scope issued by NICE	**Decision problem addressed**
Population	People with untreated advanced or metastatic RCC	Per the scope, all evidence identified was for adults
Intervention	Cabozantinib plus nivolumab (Ipsen)	Per the scope
Comparator(s)	• Pazopanib • Tivozanib • Sunitinib • Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivolumab plus ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Lenvatinib plus pembrolizumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Active surveillance	In line with the scope except that active surveillance has not been included as it is considered to happen prior to the decision node at which this model starts. Clinical advice received is that clinical decision-making first involves deciding whether or not a person would benefit from any kind of systemic therapy and then, once the decision to initiate therapy has been taken, a choice is made between available treatment options
Outcomes	• overall survival • progression-free survival • response rates • duration of response	Per the scope dependent upon data availability; limited data are available for time on treatment and time to next treatment within published literature

	• time on treatment/time to next treatment • adverse effects of treatment • health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator or subsequent treatment technologies will be taken into account	Per the scope
Subgroups	If the evidence allows the following subgroup will be considered: • intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria • prior treatment	Per the scope. Data are not available within CheckMate 9ER to explore the impact of prior adjuvant treatment on outcomes
Special considerations including issues related to equity or equality	None	None

Abbreviations: IMDC, International Metastatic RCC Database Consortium; NICE, National Institute for Health and Care Excellence; RCC, renal cell carcinoma

3.6. Description of the technology being evaluated

Cabozantinib is a multiple receptor TKI and nivolumab is a PD-1 inhibitor. The combination was granted approval for the first-line treatment of advanced RCC on the basis of the CheckMate 9ER Phase III trial[28], first by the European Medicines Agency (EMA) on 26th March 2021[29] and then Medicines and Healthcare products Regulatory Agency (MHRA) on 13th May 2021 according to information supplied by the company. The marketing authorisation holder for cabozantinib is Ipsen Pharma. The marketing authorisation holder for nivolumab is Bristol-Myers Squibb Pharma EEIG.

Cabozantinib is administered orally at a dose of 40 mg once daily. [30] Nivolumab is given intravenously at a dose of either 240 mg every 2 weeks or 480mg every 4 weeks: the former was used in CheckMate 9ER while, based upon initial expert consultation, the latter is more likely to be used in clinical practice. In line with the trial, the Summary of Product Characteristics (SmPC) [30] specifies that cabozantinib *"should be continued until disease progression or unacceptable toxicity. Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression."*

Additional information will be added to this section including the standard table once the company submission has been received.

3.7. Equality considerations

No equality issues are foreseen within this appraisal.

4. CLINICAL EFFECTIVENESS

4.1. Assessment group methods for reviewing clinical evidence

The EAG conducted a systematic literature review (SLR) to identify published evidence and real-world data sets relevant to the decision problem. The methods used were consistent with the NICE preferred methods and with best practice guidance for the conduct of SLRs. [31,32] This section provides a description of the methods used in the SLR and also presents a list of studies included.

4.1.1. Search strategies and screening process

Systematic searches were conducted to identify 1) clinical effectiveness SLRs and meta-analyses, 2) randomised controlled trials (RCTs) published since the most recent relevant systematic reviews and 3) sources of RWE. The database searches were complemented by supplemental searching, such as citation chasing, and hand-searches of grey literature sources. All data from published HTA reports included in the reviews was publicly-available; i.e. redacted data from published NICE HTA reports was not included. In cases where there were missing data in the published or submitted clinical effectiveness studies, attempts were made to contact authors. This was only done where data for an entire key outcome, Kaplan-Meier data for a key outcome or sub-group data (baseline characteristics or outcomes) were missing. A deadline for response to the initial contact of 4 weeks was imposed. The EAG are still awaiting responses from some author contact and are in the process of contacting the final set of required authors.

Search strategies were developed by an information specialist and separately quality assured by another information specialist. The search strategies used a combination of indexed keywords (e.g., Medical Subject Headings [MeSH]) and free-text terms appearing in the titles and/or abstracts of database records, and were adapted according to the configuration of each database. No limits on publication status (published, unpublished, in-press, and in-progress) were applied. The strategy used for each type of evidence included in the review is described in the following sections. The searches from NICE TA858[19] were used as a starting point for development of search terms for this appraisal. Full search strategies are supplied in Appendix 1.

Articles for the SLR and RCT searches were independently assessed for inclusion by two reviewers using the pre-specified inclusion/exclusion criteria. Discrepancies were resolved by

discussion, with involvement of a third reviewer, where necessary. All duplicate papers were double checked and excluded.

Articles for the RWE searches were assessed in a more targeted fashion by one reviewer using the pre-specified inclusion/exclusion criteria (see Section 4.1.1.3).

4.1.1.1. Search for systematic reviews and meta-analyses of clinical effectiveness evidence

Searches for relevant SLRs were undertaken in MEDLINE, Embase, Cochrane Database of Systematic Reviews (CDSR) and The International Network of Agencies for Health Technology Assessment (INAHTA). Relevant NICE technology appraisals were identified by handsearching the NICE website and were screened for further relevant studies.

The search used a combination of terms for RCC with relevant intervention terms. There were no restrictions on cancer stage or line of treatment for this search. The intervention terms were avelumab, axitinib, cabozantinib, everolimus, ipilimumab, lenvatinib, nivolumab, pazopanib, pembrolizumab, sunitinib, and tivozanib, plus relevant brand names and other alternative names.

In Medline and Embase, we used the systematic review, meta-analysis and HTA filter from The Canadian Agency for Drugs and Technologies in Health (CADTH)[33] to identify relevant records. All searches were limited from 2018 onwards, however, as the searches resulted in a high volume of hits (n=1273 after de-duplication), a decision was taken to limit screening to records published from 2020 onwards (thereby excluding 371 retrieved records published pre-2020). No language filters were used. Conference abstracts were included.

We then sought to identify the most recent, highest-quality and most comprehensive SLRs to identify RCTs relevant for this appraisal. The SLRs identified were qualitatively assessed against the following criteria:

- Is a full paper available (rather than an abstract)?
- Which line(s) of treatment were included?
- How many treatments specified within the decision problem were included within the networks?

- Were the trials included in the most recent NICE TAs for the relevant line of treatment included (TA858, TA645, TA463)?
- For SLRs looking at first-line treatments: is data presented by risk subgroup?
- Does the methods description indicate that this is a high quality SLR?

Based upon these criteria, four SLRs were identified and screened for RCTs: Heo 2022, Liao 2022, Riaz 2021 and NICE TA858. [19,34-36] The publication date of these SLRs was then used to inform the date from which to run the top-up RCT searches described in the next section.

Heo et al. presented a SLR and network-meta analysis (NMA) of OS and PFS for first-line and second-line therapies in participants with advanced RCC based upon 26 RCTs (first line: 19; second line: 9) with 13,893 participants. The networks presented included a number of treatments that are not available in the NHS, and the search excluded three treatments of interest to our decision problem: cabozantinib plus nivolumab, pembrolizumab plus lenvatinib in first-line, and everolimus plus lenvatinib for people who have been previously treated. The authors searched for trials published between 2000 and June 2020 which would be expected to capture all trials for treatments included in the decision problem for this appraisal given when development of the relevant treatments began. The review was conducted using best practice methods.

Liao et al. presented a SLR and NMA for advanced RCC treatments in the second-line setting. Nine RCTs with 4,911 participants were included. The study considered all systemic treatments used in a second-line setting and therefore identified evidence for everolimus plus lenvatinib, which was missing from the Heo et al. study. Searches were conducted from inception to July 20, 2021. The study reporting was less comprehensive than Heo et al., however, the study was included due to the broader range of treatments covered and more recent search date.

Riaz et al. present a living, interactive SLR and NMA of first-line treatments for advanced RCC. No limits on included treatments were imposed and outcomes were presented by risk score. Evidence was identified for all of the treatments of interest to the decision problem for first-line RCC except for pembrolizumab plus lenvatinib. A comprehensive search was conducted from inception by an experienced medical librarian in consultation with the principal investigator (I.B.R.). A “living” auto search with monthly updates was subsequently created with the last date of evidence included being October 22, 2020. Study selection and extraction were both semi-automated.

TA858 was the most recent NICE TA in RCC. This appraisal considered treatments in the first line setting, and searches were run in October and November 2021. All of the first-line treatments of interest were included with the exceptions of avelumab plus axitinib and cabozantinib plus nivolumab. Reporting was split by risk group. Screening and extraction was performed by two reviewers. Full search strategies were provided in the report Appendix and were used to inform the development of the searches conducted within this appraisal.

4.1.1.2. Top-up search for RCTs of clinical effectiveness evidence

A top-up search to identify RCTs published since the latest SLR search dates was conducted. The search was conducted in MEDLINE, Embase, CENTRAL (Cochrane Central Register of Controlled Trials) and trial registers (WHO International Clinical Trials Registry Platform and Clinicaltrials.gov). The search identified trials published from 2021 onwards, which allowed a reasonable overlap in time to capture RCTs published since the most recent search dates of the reviews described in section 4.1.1.1 for each line of treatment: Liao 2022 and TA858. [19,35]

We identified RCTs using the same intervention terms as used in the search for SLRs. For this search we used terms to focus on people with advanced, metastatic or otherwise later stage RCC. The Cochrane RCT filter was used to identify relevant trials in Medline and Embase. No language limits were applied. Conference abstracts were included.

We searched Scopus for subsequent data cuts of trials included in the identified SLRs, including conference abstracts. We further conducted citation searches (forward and backward citation searching) in Scopus for all additional RCTs identified that were not included in the latest SLRs. Relevant NICE technology appraisal reports were reviewed to identify any additional unredacted data that had not been subsequently published. We also hand-searched the list of published abstracts from the American Society of Clinical Oncology Genitourinary Cancers Symposium, held in San Francisco on the 16 - 18 Feb 2023 (ASCO GU 2023), to identify new trials or new data cuts of already identified trials.

Finally, health-related quality of life and patient-reported outcomes for the 30 included RCT studies were identified by reviewing the economic searches for the development of the cost-effectiveness model (see section 5.1.1). Twenty nine potentially relevant reports were identified by searching for RCT trial numbers in the economic studies Endnote database, which were then sifted down to 23 studies (covering 16 of the 30 RCTs) during full-text review.

To identify ongoing RCTs, we searched Clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP). The advanced search functionality was used for both platforms, using a combination of intervention terms, population terms, and keywords to identify RCTs (random or randomized or randomised or randomisation or randomization or RCT). No date or recruitment status limits were applied. The RCT update search of Cochrane CENTRAL (described above) also retrieved registry records.

4.1.1.3. Searches and screening for real-world evidence

In line with the recommendations in the NICE RWE framework, [37] a systematic search process was followed to identify real-world (observational) evidence to characterise the treatment pathway, the natural history of the disease and the characteristics of people with RCC treated in clinical practice. We used a four-pronged search strategy:

1. Medline and Embase: Search results for observational studies in the UK about RCC were uploaded into Endnote, followed by assessment of abstracts to identify any registry/RWE data sources used. The search combined the Scottish Intercollegiate Guidelines Network (SIGN) observational studies filter[38] and the NICE UK filter. [39] Search strategies are provided in Appendix 1. Results (n = 2,683) were exported into Endnote and screened by one reviewer using the pre-specified inclusion criteria (described below).
2. Health Data Research UK Innovation Gateway: Search terms included ‘renal cell cancer’, ‘renal cell carcinoma’, ‘kidney cancer’ or ‘kidney carcinoma’. Results were sifted on screen by one review using the inclusion criteria.
3. Web search (Google and Bing): Individual searches within each database were conducted using terms for RCC and RWE. RCC search terms were: ‘renal cell cancer’, ‘renal cell carcinoma’, ‘kidney cancer’, and ‘kidney carcinoma. RWE search terms were ‘registry’, ‘real-world data’, and ‘real-world evidence’. The first 50 results of each search were sifted on screen by one reviewer using the inclusion criteria.
4. Reviewers flagged potential evidence sources—that met the inclusion—during screening of the main clinical and economic search results.

4.1.2. Consultation with clinical experts

As part of its appraisal, the EAG will consult with clinical experts in RCC. Up to three clinical experts will be recruited and consulted for their views on topics such as disease characteristics, typical treatment pathways, disease and treatment outcomes, and treatment effect modifiers.

Experts will all be senior clinicians currently working in the NHS and/or academics with a publication record in RCC. Where feasible, experts who represent a range in expertise will be recruited, for example to represent a range of treatment settings and specialisms. Experts will be recruited in accordance with NICE conflict of interest policy; i.e. experts who are not conflicted for this appraisal will be prioritised for recruitment, and where conflicts are present, these will be declared and the EAG will endeavour to recruit an additional unconflicted expert. Expert views have been used to guide the methods outlined in this protocol, and will aid interpretation of the appraisal findings.

In addition to this consultation, a broader group of experts will be recruited to participate in an expert elicitation exercise to inform long-term OS estimates. This procedure is described in Section 5.2.

4.1.3. Inclusion and exclusion criteria

In the first round of screening, we included a) systematic reviews of RCTs b) of pharmacological treatments for advanced renal cell carcinoma c) published since 2020. We excluded reviews focusing on the efficacy of radiotherapy or surgical interventions. We then focused on the highest-quality and broadest systematic reviews to identify relevant RCTs and mapped these trials against comparators and lines of treatment to identify any gaps.

In top-up searches, we included a) RCTs b) of systemic treatments funded within the NHS (pazopanib, tivozanib, sunitinib, cabozantinib, nivolumab plus ipilimumab, lenvatinib plus pembrolizumab, axitinib, lenvatinib plus everolimus, everolimus, cabozantinib plus nivolumab, nivolumab, avelumab plus axitinib, best supportive care) c) for patients with advanced RCC d) reporting at least one outcome from overall survival, progression-free survival, time to next treatment (TTNT), time to discontinuation (TTD), response rates, adverse effects of treatment, and (HRQoL). As a protocol clarification, we also included studies with placebo as a comparator and we only included studies with relevant comparisons of drugs prescribed at the licensed doses. In addition, as a protocol deviation, we included studies with sorafenib as a comparator. This is because past technology appraisals have acknowledged the importance of sorafenib as a linking treatment in evidence networks and we also anticipate needing to use sorafenib as a linking treatment.

Further details on these inclusion/exclusion criteria used for SLRs and RCTs are presented in Table 2.

Table 2: Inclusion and exclusion criteria

PICOS item	Include	Exclude
Population	Studies of participants with advanced (unresectable Stage 3 or Stage 4) RCC at any treatment line	Studies of participants with early stage (not advanced) RCC
Intervention	Round 1 (systematic reviews): any pharmacological treatment for advanced RCC used in the systemic setting Round 2 (RCTs and extensions of RCTs): cabozantinib plus nivolumab, pazopanib, tivozanib, sunitinib, cabozantinib, nivolumab plus ipilimumab, lenvatinib plus pembrolizumab, axitinib, lenvatinib plus everolimus, everolimus, nivolumab, avelumab plus axitinib*, Sorafenib and placebo were included as linking treatments for use in the NMA	Any other treatments not listed under inclusion Treatments used in the adjuvant setting
Comparator	Any of the other interventions listed above (i.e. head-to-head studies) Dose comparison studies Usual care / physicians' choice / BSC / placebo	Non-pharmacological treatments only
Outcomes	Studies reporting at least one outcome from: • OS • PFS • time to next treatment • time on treatment • response rates • duration of response • AEs of treatment¥ • HRQoL	Studies not reporting an included outcome
Study design	Round 1: systematic reviews of RCTs published since 2020 Round 2: RCTs. The most recent conference abstract for each intervention and outcome will be included unless a full journal article is available	Round 1: systematic reviews that did not contain RCTs, systematic reviews of treatment effect modifiers. Round 2: non-randomised trials, observational studies, case reports, editorials and commentaries

Abbreviations: AE, adverse events; BSC, best supportive care; HRQoL, health-related quality of life; OS, overall survival, PFS, progression-free survival; RCT, randomised controlled trials

Notes: * as belzutifan was included within the NICE draft scope it was included within the search terms for the searches conducted, these studies will, however, not be included during screening ¥ we will extract data for Grade 3+ treatment-emergent adverse events and the total number of treatment-emergent adverse events leading to discontinuation. Additional lower grade adverse events of interest may be extracted following clinical advice

We used the following inclusion criteria to identify sources of potential RWE:

- Population: advanced RCC
- Intervention: any pharmacological treatment for advanced RCC used in the systemic setting
- Data collected: OS, PFS, TTD, TTNT, HRQoL, current treatment pathways (sequences) being used, prognostic variables, risk scores, health costs
- Geography: UK
- Time: collection of data within the last 10 years with a focus on datasets including more recent data (2018 onwards)

4.1.4. Data extraction and quality assessment strategy

Data extraction of the clinical effectiveness evidence is at trial level. All relevant published evidence for a given trial is extracted in one, single entry in the data extraction matrix. Included clinical effectiveness studies (identified via SLRs and top-up searches) and included observational studies were extracted by one reviewer into a bespoke database and checked by a second reviewer. Quality assurance of data extraction is still ongoing. The data extraction grid is provided in Appendix 2. Discrepancies were resolved by discussion, with the involvement of a third reviewer if necessary. Extraction of outcome data is ongoing pending receipt of company submissions. For time to event outcomes, we will extract both summary hazard ratios from the last data cut. Digitisation of curves using standard methods (e.g. the Guyot algorithm) is ongoing, assuming censoring linearly across time intervals.

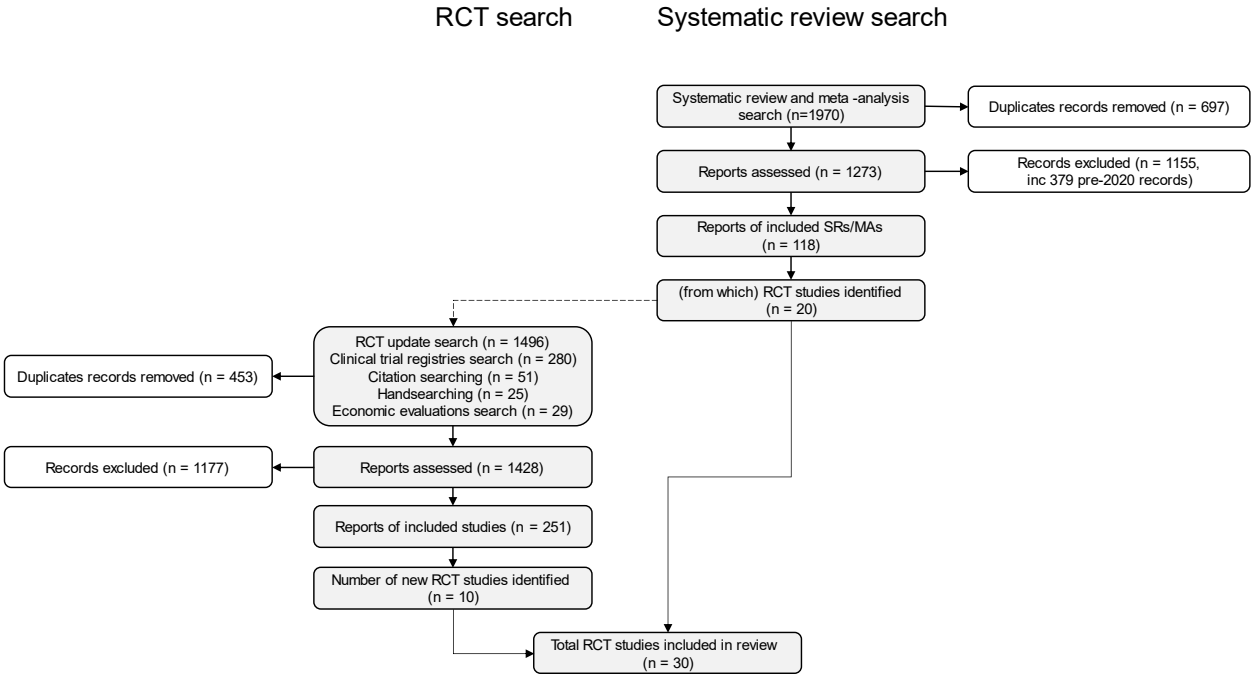
Where data are missing in the published or submitted clinical effectiveness studies, we are attempting to contact authors. This will only be done where data for an entire key outcome, Kaplan-Meier data for a key outcome or subgroup data (baseline characteristics or outcomes) are missing. A deadline for response to the initial contact of 4 weeks will be imposed. Additional time might be allowed should the author be able to supply the data requested, but without impact on the broader timelines for this appraisal.

Quality assessment of included RCTs will be undertaken using the standardised criteria used by NICE in submissions to its HTA programme. This will also include appraisal of stakeholder evidence submitted.

4.1.5. Results of the searches

Figure 7 provides an overview of the clinical review searches for SLRs and RCTs. PRISMA diagrams for the individual SLR (Figure 17) and RCT searches (Figure 18) can be found in Appendix B. In total, 118 SLRs and meta-analyses were identified, and 30 RCTs—20 identified from the SLRs, and a further ten from the RCT top up search and other supplementary search techniques.

Figure 7: Overview of clinical effectiveness searches



Abbreviations: RCT, randomised control trials; SR, systematic reviews; MA = meta-analyses

The search and screen for RWE identified four relevant online databases and eleven published reports that contained details of potentially relevant data sources for follow up (Table 3).

Table 3: Identified potential sources of RWE

Online databases		
#	**Name**	**Link**
#1	National Cancer Registration and Analysis Service (NCRAS) [40]	https://www.cancerdata.nhs.uk/
#2	Systemic Anti-Cancer Therapy (SACT) data set[41]	http://www.chemodataset.nhs.uk/
#3	Clinical Practice Research Datalink (CPRD) [42]	https://cprd.com/

#4	Hospital Episode Statistics (HES) [43]	https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics

Potentially relevant data sources (identified from publications)

#	Name	Link
#5	RECCORD (Renal Cell Carcinoma Outcomes Research Dataset) registry[44]	https://pubmed.ncbi.nlm.nih.gov/26489444/
#6	REMARCC (Registry for Metastatic RCC) [45]	https://pubmed.ncbi.nlm.nih.gov/33384274/
#7	IMDC International mRCC Database Consortium[46]	https://www.imdconline.com/
#8	IQVIA real world oncology cross-sectional survey data[47]	https://pubmed.ncbi.nlm.nih.gov/29466966/
#9	Patterns of care and outcomes of metastatic renal cell carcinoma (mRCC) patients (pts) with bone metastases (BM): A UK multicenter review[48]	https://doi.org/10.1016/j.annonc.2022.07.1566
#10	Real-world Experience With Sunitinib Treatment in Patients With Metastatic Renal Cell Carcinoma: Clinical Outcome According to Risk Score[15]	https://pubmed.ncbi.nlm.nih.gov/32586677/
#11	Avelumab plus axitinib in advanced renal cell carcinoma (aRCC): 12-month interim results from a real-world observational study in the United Kingdom[49]	https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.6_suppl.301
#12	Cabozantinib and axitinib after VEGF therapy in patients with aRCC: A retrospective cohort study[50]	https://www.annalsofoncology.org/article/S0923-7534(21)02290-0/fulltext
#13	Real world experience of nivolumab therapy in metastatic renal cancer patients: A 3 year multi-centre review[51]	https://www.annalsofoncology.org/article/S0923-7534(19)59175-X/fulltext
#14	Treatment patterns and health outcomes in metastatic renal cell carcinoma patients treated with targeted systemic therapies in the UK[14]	https://pubmed.ncbi.nlm.nih.gov/32680483/
#15	Real-world outcomes of immune-related adverse events in 2,125 patients managed with immunotherapy: A United Kingdom multicenter series[52]	https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.7065

Of the four online databases identified, only the National Cancer Registration and Analysis Service (NCRAS) provides publicly accessible data for the advanced RCC population. The NCRAS forms part of the National Disease Registration Service (NDRS) in NHS Digital. On 1 October 2021, responsibility for the management of the NDRS transferred from Public Health England (PHE) to NHS Digital. The EAG have extracted publicly available data from the NCRAS, specifically the 'Get Data Out' programme. The 'Kidney' dataset contains information on incidence, treatment rates, survival, routes to diagnosis (and other key outcomes) for patients with malignant kidney cancer in England from 2013 to 2019. Whilst these data are useful, the EAG acknowledge that this dataset should be interpreted with caution as it is subject to several limitations, including the following.

- The staging system for kidney cancers changed from TNM 7 to TNM 8 between 2017 and 2018 diagnoses. Changing the definition likely reduces the number of stage 2 tumours and increases the number of stage 3 tumours, therefore care must be taken when analysing the GDO data as a time series.
- Registration of 2019 tumours were completed during the COVID-19 pandemic. This resulted in reduced access to usual data sources and a decrease in data quality in some fields. This is evidenced by an increase in 'stage unknown' tumours, and a corresponding decrease in other stage groups.
- There are censored/missing KM survival data for the most recent years i.e. overall survival data collected in 2019 is only available for up to 12-months (2020). Whilst it may be reasonable to expect that immuno-oncology combinations, which have recently entered clinical practice, may lead to improved survival rates for patients, there is a lack of long-term overall survival data which introduces uncertainty.

The data we would require from the systemic anti-cancer therapy dataset (SACT), clinical practice research datalink (CPRD) and hospital episode statistics dataset (HES) for this project are not available in the public domain and cannot be accessed within the timescales of this project.

We contacted authors for each of the eleven potentially relevant data sources identified from publications. We allowed three weeks for a response with one chasing email sent. The most promising discussions we have had were with the authors of sources #9, #11, #13 and #15, with whom we are currently discussing data sharing arrangements. Other potential sources were either deemed out of scope (#6 and #7), unavailable (#8), or did not respond.

Finally, it is possible that the NICE team will gain and share access to data generated specifically for this project via a healthcare data analytics company.

4.2. Critique of trials of the technologies of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

This will largely be populated upon receipt of company submission. This section contains information on publicly available data only at present and only information on data retrieved via searches rather than a detailed critique which will require input from the company submission for context.

4.2.1. Included studies

In total, we identified 30 trials of which six are ongoing and are addressed below in Section 4.4. The remaining 24 trials are described below and summarised in Table 4.

Table 4: Clinical evidence included

Study name	Lead reference	Population	Clear cell type (%)	Risk score (IMDC or MSKCC)	Trt line	Comparison
ASPEN (NCT01108445)	Armstrong 2016, Lancet Oncol[53]	Advanced and Metastatic (N=108)	0	Mixed	1st line*	SUN vs EVE
AXIS (NCT00678392)	Rini 2011, Lancet[54]	Advanced and Metastatic (N=723)	100	Mixed	2nd line	AXI vs SORA
BERAT (EUDRACT 2011-005939-78)	Grunwald 2022, Oncol Res Treat[55]	Metastatic (N=22)	NR	NR	2nd line	TKI (AXI/SUN) vs EVE
BIONIKK (NCT02960906)	Vano 2022, Lancet Oncol[56]	Metastatic (N=202)	100	Mixed	1st line+	NIV vs NIV/IPI, NIV/IPI vs VEGFR-TKI (SUN/PAZ)
CABOSUN (NCT01835158)	Choueiri 2018, Eur J Cancer[57]	Metastatic (N=157)	100	Intermediate and poor	1st line	CAB vs SUN
CheckMate 025 (NCT01668784)	Motzer 2015, NEJM[58]	Advanced and Metastatic (N=821)	100	Mixed	2nd and 3rd line	NIV vs EVE
CheckMate 214 (NCT02231749)	Motzer 2018, NEJM[59]	Advanced (N=1096)	100	Mixed	1st line	NIV+IPI vs SUN
CheckMate 9ER (NCT03141177)	Choueiri 2021a, NEJM[28]	Advanced (N=651)	100	Mixed	1st line	NIV/CAB vs SUN
CLEAR (NCT02811861)	Motzer 2021b, NEJM[60]	Advanced (N=1069)	100	Mixed	1st line	PEM+LEN vs LEN+EVE vs SUN
COMPARZ (NCT00720941)	Motzer 2013, NEJM[61]	Metastatic (N=1110)	100	Mixed	1st line	PAZ vs SUN
CROSS-J-RCC (NCT01481870)	Tomita 2020, Clin Genitourin Cancer[62]	Metastatic (N=120)	100	Favourable and intermediate	1st line	SUN vs SORA
ESPN (NCT01185366)	Tannir 2016, Eur Urol[63]	Metastatic (N=72)	16.7	Mixed	1st line*	EVE vs SUN
Hutson et al, 2017 (NCT00920816)	Hutson 2013, Lancet Oncol[64]	Metastatic (N=288)	100	Favourable and intermediate	1st line*	AXI vs SORA
JAVELIN RENAL 101 (NCT02684006)	Motzer 2019, NEJM[65]	Advanced (N=886)	100	Mixed	1st line	AVE/AXI vs SUN
METEOR (NCT01865747)	Choueiri 2015, NEJM[66]	Advanced and Metastatic (N=658)	100	Mixed	2nd and 3rd line	CABO vs EVE
NCT01136733 (NCT01136733)	Motzer 2015, Lancet Oncol[67]	Advanced and Metastatic (N=153 (101 relevant))	100	Mixed	2nd line	EVE+LEN vs EVE
RECORD-1 (NCT00410124))	Motzer 2008 Lancet[68]	Metastatic (N=410)	100	Mixed	2nd and 3rd line	EVE vs PLACEBO
RECORD-3 (NCT00903175)	Motzer 2014 J Clin Oncol[69]	Advanced and Metastatic (N=471)	85	Mixed	1st line*	SUN vs EVE
SWITCH (NCT00732914)	Eichelberg 2015 Eur Urology[70]	Advanced and Metastatic (N=365)	87	Favourable and intermediate	1st line	SUN vs SORA

Study name	Lead reference	Population	Clear cell type (%)	Risk score (IMDC or MSKCC)	Trt line	Comparison
SWITCH II (NCT01613846)	Retz 2019 Eur J Cancer[71]	Advanced and Metastatic (N=377)	87	Favourable and intermediate	1st line	PAZO vs SORA
SWOG 1500 (NCT02761057)	Pal 2021 Lancet[72]	Other mixed (N=152 (94 relevant))	0	Mixed	1st line	CABO vs SUN
TIVO-1 (NCT01030783)	Motzer 2013 J Clin Oncol[73]	Metastatic (N=517)	100	Favourable and intermediate	1st and 2nd line	TIVO vs SORA
TIVO-3 (NCT02627963)	Rini 2020 Lancet Oncol[74]	Advanced and Metastatic (N=350)	100	Mixed	3rd and 4th line	TIVO vs SORA
VEG105192 (NCT00334282)	Sternberg 2010 J Clin Oncol[75]	Advanced and Metastatic (N=435)	100	Favourable and intermediate	1st and 2nd line¥	PAZ vs PLACEBO

Abbreviations: AXI, axitinib; AVE, avelumab; CABO, cabozantinib; EVE, everolimus; LEN, Lenvatinib; NIV, nivolumab; PAZ, pazopanib; PEM, pembrolizumab; RCT, randomised controlled trial; SORA, soratenib; SUN, sunitinib; TIVO, tivozanib; TKI, tyrosine kinase inhibitor; trt, treatment; VEGFR, vascular endothelial growth factor receptors; vs, versus

* These trials are not included in the first-line networks as they do not contain two treatments (or one treatment and a linking treatment) which can be used at first line in England and Wales

+ This trial is not currently included in the first-line network because it includes a non-standard design

¥ This trial is not included in the first-line network as no other trials compared to placebo and therefore inclusion did not add any value to the network

4.2.2. Description and critique of the design of the studies

Of the 24 included RCTs, the earliest participants were recruited in 2006, with the most recent data cuts in published records drawing from December 2019. Trials included as few as three and as many as 200 centres, with at least 14 trials including UK centres; and had sample sizes across arms comparing relevant treatments of between 22 and 1,110 participants.

4.2.2.1. Design of the studies

Of the 24 included trials, 20 were parallel trials and four were crossover trials. The four crossover trials sought to test two-drug sequences characterised by treatment with the first drug to progression; for example, in SWITCH, [70] patients were randomised to sunitinib followed by sorafenib after progression, or sorafenib followed by sunitinib after progression. All 20 parallel trials tested individual treatments to progression or death, with post-progression treatment generally not directly specified (though in METEOR, everolimus patients could cross over to cabozantinib[66]; similarly, in ESPN patients could cross over to everolimus).

Though some RCTs included independent masked review (e.g. of progression status), 20 trials were described by study authors as open-label; the remaining trials were distributed as one double-blind, two single-blind, and one triple-blind. Though three trials did not provide sufficient information, 21 trials used stratified randomisation, generally on the basis of risk category and, where relevant, prior treatment.

Only one trial did not report any industry funding.

4.2.2.2. Population

Inclusion/ exclusion criteria

All trials included participants aged 18 years or older, with histologically confirmed RCC measurable via RECIST guidelines, and with participants having adequate performance status (generally defined as ECOG performance status of 0 or 1, or as Karnofsky Performance Score of 70% or above). All trials required participants to have advanced or metastatic RCC, though the exact form of wording varied including within different reports of the same trial. Only one trial, SWOG 1500[72], permitted inclusion of participants with locally advanced cancer. Exclusion criteria related principally to other health parameters, such as controlled hypertension and adequate organ function; in addition, 20 trials reported explicit exclusion criteria with respect to brain and central nervous system metastases.

Additional criteria related principally to prior lines of treatment and risk group. These are discussed under baseline characteristics.

Baseline characteristics

Histology. Of the 24 trials, 17 included patients with clear cell RCC only, or RCC with a clear cell component. A further five trials included participants with mixed histologies. The remaining two trials specifically targeted participants with predominantly non-clear-cell RCC histology.

Risk distribution. Risk distribution was measured by a combination of IMDC and MSKCC risk scores. For convenience, both sets of risk scoring methods are described as producing risk score classes as 'favourable', 'intermediate' or 'poor'. Two trials did not enrol any participants assessed as having poor risk, and a further five trials enrolled a very low number of participants assessed as being at poor risk (i.e. ≤5% of the trial sample). One trial only enrolled participants assessed as being at intermediate or poor risk. Proportions of participants assessed as being at favourable risk ranged in trials from 0 to 52%, while for intermediate risk, participants proportions ranged from 37% to 81%. Proportions of participants assessed as being at poor risk ranged from 0% to 40%.

Prior lines of systemic therapy. Of 24 trials, 17 RCTs included participants for whom the study drug was classed as their first line of systemic therapy. Of these 17 trials, 14 were only in participants receiving first-line treatment. The remaining three trials enrolled patients to receive first-line and second-line treatments; for these trials, the proportion of patients receiving their first systemic treatment ranged from 93% to 53%.

Correspondingly, 10 trials enrolled participants receiving second-line or later therapy. Distinguishing between participants receiving second-line and third-line systemic treatments was complicated by the fact that trials inconsistently included participants on the basis of prior lines of treatment belonging to a specific class. However, data presented in included studies indicated that beyond three trials enrolling a mix of first-line and second-line patients, an additional two trials enrolled only participants for the second line of treatment. Of the remaining five trials, four enrolled participants across second-line and third-line, with ranges of second-line treatment between 20% and 72%; and one trial enrolled only participants at the third and fourth lines of therapy, with 60% of participants at third line.

Prior systemic TKI or immunotherapy. Data on the proportions of participants with prior systemic TKI were inconsistently reported. Of the 11 trials reporting data on this point, five trials

enrolled only participants with prior TKI, one enrolled a blend of participants with and without prior TKI and five trials enrolled participants only without prior TKIs. Data on the proportions of participants with prior immunotherapies were also inconsistently reported. Of the 10 trials reporting data on this point, four enrolled participants only without prior immunotherapies.

Prior surgery. Data on prior nephrectomy were reported for 18 trials. One trial only enrolled participants with prior nephrectomy. In every other trial reporting data for this point, the majority of participants had prior nephrectomy, with a minimum of 67%.

4.2.2.3. Interventions and comparators

Interventions and comparators were distributed unevenly across the included trials. Our commentary focuses here only on relevant arms in included trials. There was evidence from at least one trial for all relevant active interventions. No trials used current care, investigator's choice or best supportive care as a comparator, but placebo was used as a comparator in two trials. Sunitinib was the most commonly represented treatment, used as a comparator on 14 trials, followed by single-agent everolimus in eight trials and sorafenib (used as a linking treatment) in seven trials. Pazopanib appeared in four trials, and single-agent axitinib and single-agent cabozantinib each appeared in three trials. Nivolumab, combined nivolumab and ipilimumab, tivozanib, and combined lenvatinib and everolimus each appeared in trials twice. Combined avelumab and axitinib, combined cabozantinib and nivolumab, and combined pembrolizumab and lenvatinib each appeared in trials once.

4.2.2.4. Outcomes

The outcomes reported in the 24 trials are summarised in Table 5.

Our account of outcomes is derived from publicly available trial reports. Full scrutiny of outcomes reported in HTA reports and publications identified in the utilities literature review (reported within Chapter 5) will be included the final report.

Overall survival

Overall survival (OS) was measured in all included trials. Details of follow-up duration were reported for 17 trials, and in a range of ways. Where trials reported the time to final follow-up (n=8), this was below two years in one case and up to seven years in one case; five trials had final follow-ups of between two and four years. An additional trial reported minimum follow-up of 13 months. The remaining eight trials reported median or average follow-up period. Four trials

reported median or average follow-up of less than two years, one a median follow-up of two years and a final three trials a median follow-up of between three and six years. Because most analysis protocols were event-driven and included interim analyses, OS data were of variable maturity between trials, highlighting the need for extrapolation.

Adjustment for crossover and treatment-switching was inconsistently addressed in included trials. In trials with a crossover design, OS was not adjusted as the goal of the analysis was to capture the crossover between two different drugs. Treatment-switching adjustments to OS were reported in relatively few trials. Where subsequent treatments were reported, these were inconsistently aligned with UK practice, often making use of treatments (e.g. sorafenib) that are not part of UK treatment pathways. Information on subsequent treatments forming sequences that would be 'disallowed' in UK practice (e.g. immuno-oncology therapies followed by immuno-oncology therapies) was only inconsistently presented across trials.

Progression-free survival

Progression-free survival (PFS) on first treatment was also included in all 24 trials. Because an important element of PFS is monitoring of disease status, the tumour scan frequency used in the trials were extracted. In the 20 trials reporting tumour scan frequency, seven used a based frequency of eight weeks, and six used a base frequency of every 12 weeks or three months (with one including an interim scan after six weeks on treatment). Two trials scanned every eight weeks in the first year of study treatment with every 12 weeks thereafter. Two trials scanned 12 weeks after randomisation, then took scans every six weeks for a period of time (up to 13-14 months post-randomisation) and then every 12 weeks thereafter. Two trials scanned at weeks 6 and 12, and then every eight weeks. One trial scanned every six weeks until week 12 and then every eight weeks until progression. Three trials described additional scan frequency related to bone and brain metastases where relevant.

Additional time-to-event outcomes

Three trials reported time to progression (TTP) outcomes in publicly available trial reports, including one reporting time to deterioration on treatment as a composite outcome. Three trials also reported TTD outcomes. No trials reported TTNT.

Duration of response and response rate

Duration of response was reported in 12 trials. Response rate was reported in 22 trials.

Adverse events

Adverse events incidence and prevalence were reported in some form for all 24 trials. This generally included reporting of most common adverse events, though discontinuation due to adverse events was also reported for nearly all trials in some form.

Health-related quality of life and patient-reported outcomes

Health-related quality of life outcomes were identified for 16 trials. Utility data identified is presented in the later sections relevant to the economic analysis (Section 5.3.7.1).

Table 5: Outcomes reported by RCTs included in the review

Trial name	OS	PFS	TTP	TTD	Duration of response	Response rate	Adverse events	HRQoL
ASPEN	X	X				X	X	X
AXIS	X	X			X	X	X	X
BERAT	X	X				X	X	X
BIONIKK	X	X			X	X	X	
CABOSUN	X	X				X	X	
CheckMate 025	X	X			X	X	X	X
CheckMate 214	X	X			X	X	X	X
CheckMate 9ER	X	X				X	X	X
CLEAR	X	X			X	X	X	X
COMPARZ	X	X			X	X	X	X
CROSS-J-RCC	X	X		X	X	X	X	
ESPN	X	X					X	
Hutson et al, 2017	X	X	X*		X	X	X	X
JAVELIN RENAL 101	X	X				X	X	X
METEOR	X	X			X	X	X	
NCT01136733	X	X			X	X	X	X
RECORD-1	X	X				X	X	X
RECORD-3	X	X			X		X	X
SWITCH	X	X	X	X		X	X	
SWITCH II	X	X	X	X		X	X	X
SWOG 1500	X	X				X	X	
TIVO-1	X	X				X	X	X
TIVO-3	X	X				X	X	
VEG105192	X	X			X	X	X	X
TOTAL	**24**	**24**	**3**	**3**	**12**	**22**	**24**	**16**

*Time to treatment failure

4.3. Planned indirect comparisons

4.3.1. Methods

RCTs will be synthesised using appropriate meta-analysis methods. Evidence networks for each outcome will be formed by decision point on the pathway (i.e. line of treatment or class of prior treatment), combining second, third and fourth line RCC if need be due to similar comparator sets.

Feasibility of network meta-analyses (NMAs) will be considered by examining where possible the distribution of likely effect modifiers (e.g. age, sex, disease characteristics, subsequent therapies, IMDC prognostic risk category, whether previously treated (first line or second+ line), whether the patient had a prior nephrectomy, number of metastatic sites, number of bone metastases) over the networks. The list of potential effect modifiers will be further informed by examining trial results (interactions in forest plots), any relevant discussion from TA858, and information in the company submission.

Separate networks will be formed based on IMDC risk subgroup, stratified by line of treatment (1st line or 2+ line) and for first line treatment.

If the network contains a clear reference treatment (placebo or standard of care or a central node) then baseline risk will be compared across trials using PFS in the reference treatment. The baseline risk will serve as a proxy for treatment effect modifiers across the trials, some of which may not have been measured or collated. Heterogeneity in baseline risk may point to variation in the distribution effect modifiers over the network, and therefore potential bias in network-based treatment effect estimates.

The set of selected trials from the search process (4.1.5) were processed according to steps two and three of the algorithm outlined by Dias et al. [76] p13, namely: (2) identify all the trials that compare two or more comparators in the population of interest (3) remove trial arms that are not comparators of interest from trials with more than two arms.

Where necessary, connecting nodes were introduced which function to connect networks but do not in themselves represent comparators of interest, similar to the process in TA858. [19] As described above, these nodes principally related to sorafenib and placebo.

NMAs will be carried out for the following time-to-event outcomes: PFS and OS. Investigations on the feasibility of time-to-event NMAs for time-on-treatment and time-to-next-treatment indicated insufficient studies available.

Continuous and binary outcomes will further be grouped with respect to similarity of follow-up times and combined using standardised mean differences or odds ratios, as appropriate. Time to event outcomes will be analysed using two strategies: one primary and one exploratory. The exploratory strategy, for all time-to-event outcomes, will rely on hazard ratios from longest follow-up combined after log transformation using an inverse variance method.

The primary strategy, which will focus on progression-free survival as a priority outcome, will use a parametric modelling method.

The first strategy used fractional polynomial analyses as, based on previous appraisals in RCC, it is expected that there may be issues in justifying proportional hazards for all endpoints. Model selection compared first and second-order fractional polynomials drawn from the set of powers defined by −2, −1, −0.5, 0, 0.5, 1, 2, 3 as standard. [77]

Pseudo-individual patient data (IPD) data for survival were requested from the submitting company who provided PFS and OS data for a subset of the EAG network. Further curves were digitised by the EAG. Grouped survival data were then formed in time intervals. The time interval for grouping has not been determined but is planned to be of one week (coincident with the model cycle length), or four weeks.

Model selection used frequentist fixed effects models, identifying a candidate set of 'most likely' models on the basis of visual fit to observed data, clinical plausibility including elicited landmark survival estimates and biological considerations and statistical fit using Akaike Information Criterion (AIC). [78]

A Bayesian analysis of selected models will be carried out introducing random effects. Random effects will only be considered on the basis of 'time-invariant' heterogeneity, that is only using between-study variance on intercept terms. [77] The general framework will be to use random effects in a Bayesian framework with Markov chain Monte Carlo estimation, including informative priors from Turner (2015) [79] if available and appropriate and vague or weakly informative priors otherwise. Turner 2015 offers priors for a set of generic scenarios in healthcare and associated types of outcomes. Estimation will use two chains of 100,000

iterations with 20,000 iterations discarded as burn-in. Bayesian model comparisons will use Deviance Information Criterion (DIC). Convergence will be assessed using standard methods, including autocorrelation and Brooks-Gelman-Rubin diagnostic plots. Inconsistency will be assessed for each network using DIC estimates.

If the fractional polynomial method generates inappropriate or clinically implausible results, estimates from each trial will be meta-analysed using a multivariate strategy[80] (i.e. allowing two-dimensional treatment effects) drawing on parametric distributions (e.g. Weibull, log-normal, log-logistic). The most appropriate distribution will be chosen for each network on the basis of visual fit across included trials, DIC scores and clinical plausibility of projections against landmark survival (e.g. five years).

It is considered unlikely that OS data will be identified for untreated patients with a pathway in line with UK practice due to the predominance of the use of more than one line of immuno-oncology within trials in the literature. Synthesis of overall-survival data using methods accounting for time-varying hazards will only be conducted if sufficient data are identified either without such issues or with adjustment conducted for subsequent therapy use outside of UK practice. A basic meta-analysis of hazard ratios will instead be conducted and used for validation of the decision model rather than direct model input in the base case.

4.3.2. Critique of trials identified and included in the indirect comparisons

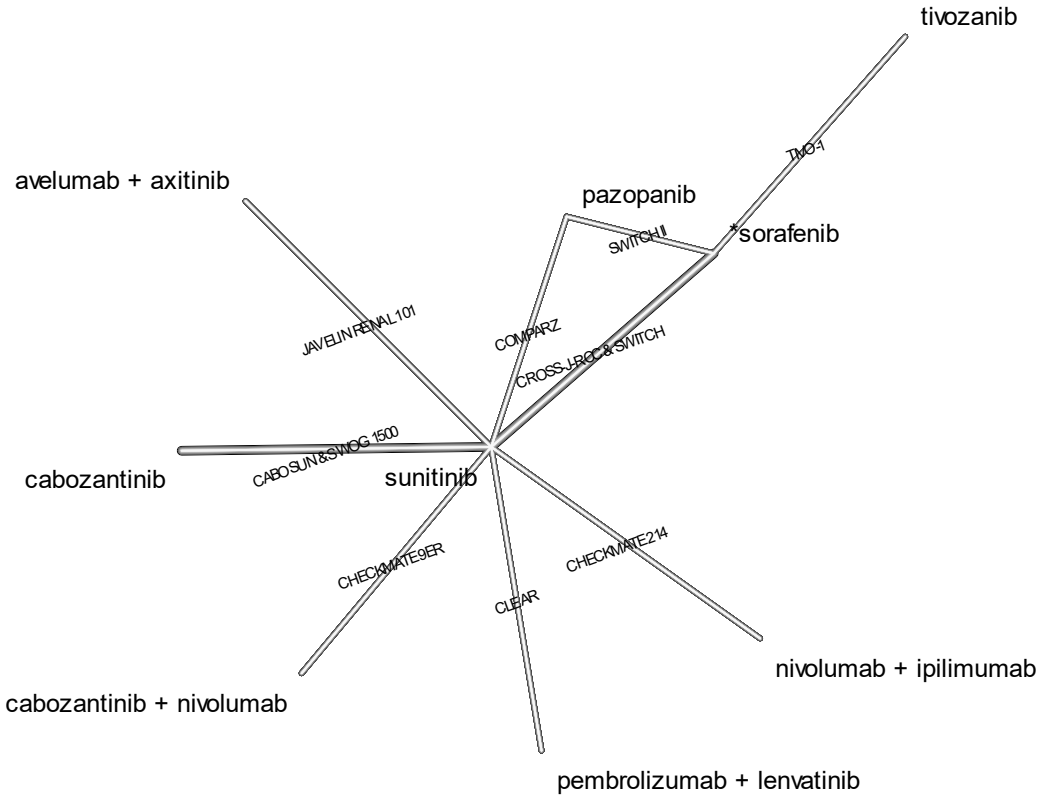
Six trials that are ongoing and yet to report were excluded (section 4.4). The majority of included trials were associated with either first or second+ line populations, but in three trials the study population was mixed. In two trials (VEG105192[75] and TIVO-1[73]), analyses by line of treatment were available. In SWOG 1500[72], 93% of participants were first line and this was treated as a first line study.

Networks were formed for first and second+ line treatments for the outcomes OS, PFS and ORR, taking into account availability of information (as HR, KM curves or response rates), and at first line for two IMDC risk categories: intermediate/poor and favourable. Network diagrams for first line PFS and OS (all risk) are shown in Figures 4 and 5. Other networks in draft form are supplied in Appendix E.

Many networks are not complete. Following the precedent in TA858 and other previous RCC appraisals, two treatments (sorafenib, placebo) were introduced as potential connecting nodes. At first line, for PFS (Figure 4), this connects tivozanib and results in a complete network, but for

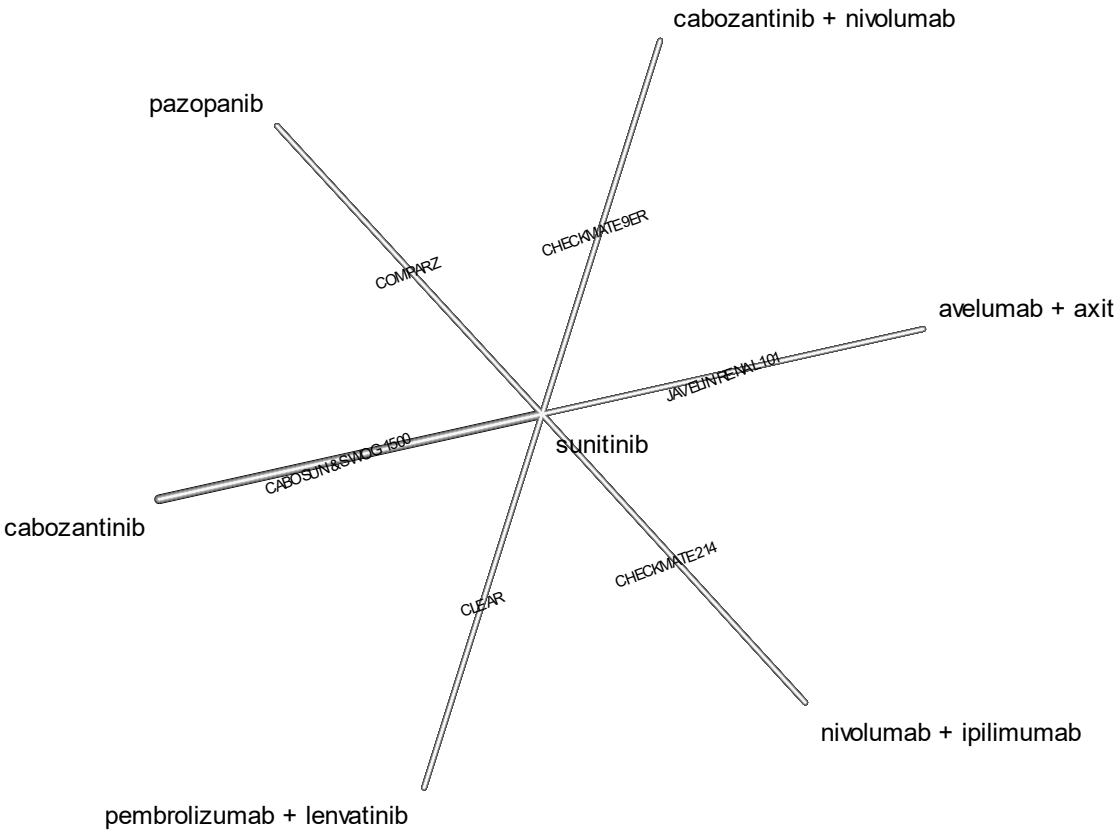
OS (Figure 5), tivozanib is excluded. This is in line with TA858 where the EAG considered that it was not possible to connect tivozanib to the OS network as OS data from patients receiving first-line treatment were not available from the CROSS-J-RCC and SWITCH trials which would have allowed connect to the TIVO-1 trial. This is likely due to the design of these trials (patients switch to the treatment they did not initially receive on progression). This is not considered to be a major issue given that the base case model structure does not use first-line OS data and previous appraisals have considered that tivozanib is at best similar to pazopanib and sunitinib (TA858, TA645). The full results for excluded treatments with and without these connecting nodes is shown in the table in Appendix E.

Figure 8: Network diagram for PFS with summary HR at first line



* Nodes with an asterisk are connecting nodes not comparators of interest.

Figure 9: Network diagram for OS with summary HR at first line



* Nodes with an asterisk are connecting nodes not comparators of interest.

As can be seen in Figure 8 and Figure 9, for first line treatments sunitinib acts as a central node for all comparators of interest, with the exception of tivozanib. Survival data (PFS) for the sunitinib arms across the first line network is shown in Figure 10. Note that some digitisations were supplied at an earlier stage and may be updated with the final data-cut. There is some indication in the plot of anomalous PFS in the sunitinib arm of CheckMate214, where PFS is elevated compared with other trials in the network, and also SWOG and ESPN, where PFS is lower. The trial and patient characteristics are yet to be fully examined to interpret these anomalies.

Summary information for select potential effect modifiers is shown in Table 6. For the final report, potential effect modification across the network will be discussed narratively with reference to evidence summaries, including extensions and interpretation of the summary table

of effect modifiers, and graphs of the network overlaid with pie charts (cf. figures 4 and 5 of Cope et al [81]).

Figure 10: Survival data (PFS) for the central node (sunitinib) of the first line network

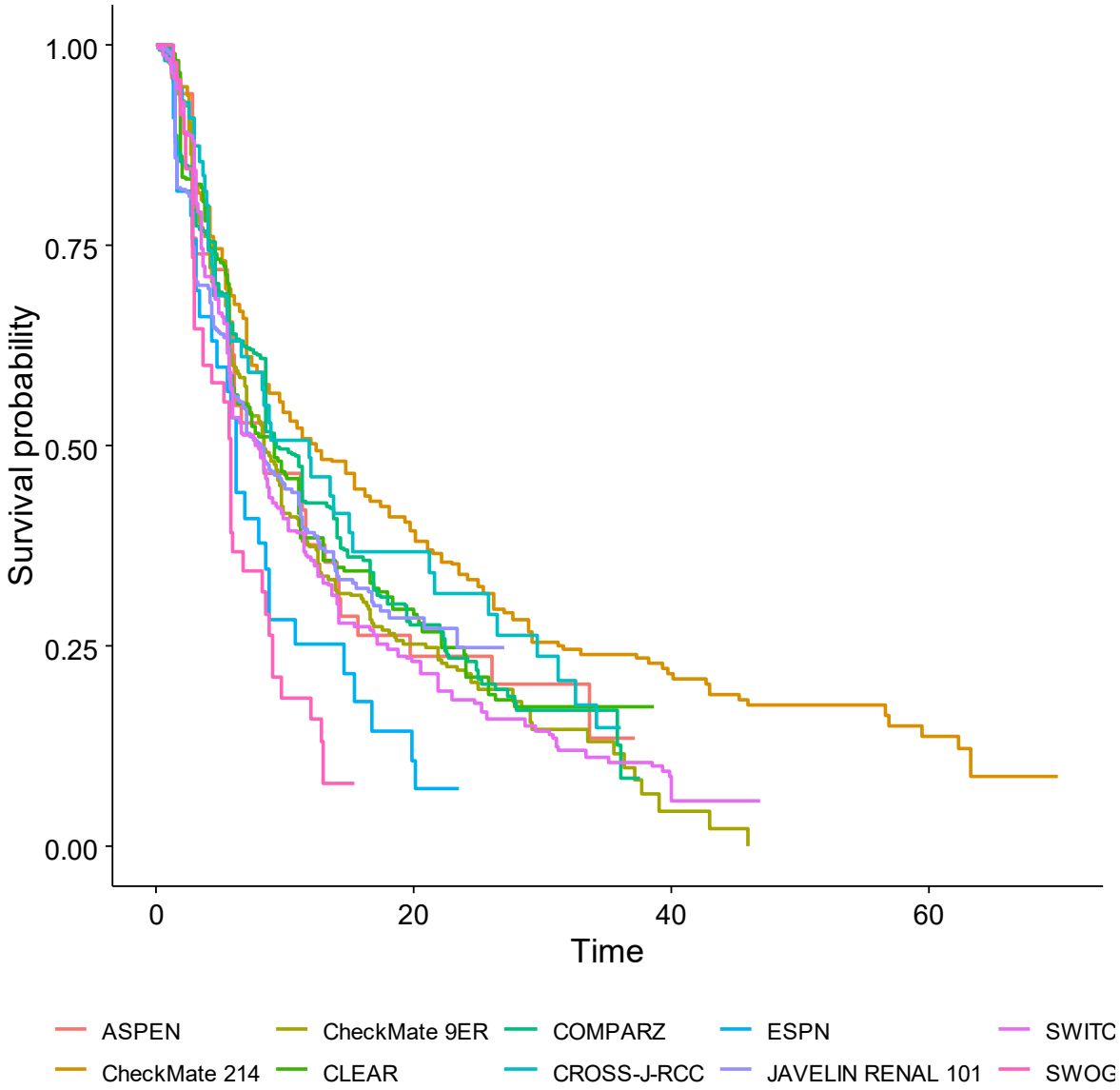


Table 6: Summary information for select effect modifiers

Trial name	Age (median) *	IMDC (%)¤			Line		Bone metastases (%) *	% clear cell
		Favourable	Intermediate	Poor	1st	2nd+		
ASPEN	63	27	60	13	100	0	24 | 26	0
AXIS	61 | 61	20	64	16	0	100	NR	100
BERAT	55	Included patients with up to 2 risk factors, split between favourable and intermediate not reported		0	0	100	NR	NR
BIONIKK	59-69	30	50	20	100	0	NR	100
CABOSUN	63	0	81	19	100	0	NR	100
CheckMate 025	62	36	49	15	0	100	18	100
CheckMate 214	62 | 62	23	61	16	100	0	20 | 22	100
CheckMate 9ER	62 | 61	23	57	20	100	0	NR	100
CLEAR	64 | 62 | 61	32	55	10	100	0	24 | 24 | 27	100
COMPARZ	61 | 62	27	59	11	100	0	NR	100
CROSS-J-RCC	67 | 67 | 66	21.7	78.3	0	100	0	23 | 33	100
ESPN	58 | 60	10	74	16	100	0	20 | 33	16.7
Hutson et al 2017	58 | 58	51	43	3	100	0	29 | 25	100
JAVELIN RENAL 101	62 | 61	22	62	16	100	0	NR	100
METEOR	62 | 63	46	42	13	0	100	22	100
NCT01136733	61	23	37	40	0	100	27	100
RECORD-1	61	29	56	14	0	100	35	100
RECORD-3	62	29	56	15	100	NA	23	85
SWITCH	65	42	55	0.5	100	0	15	87
SWITCH II	68 | 68	49	48	2	100	0	20	87
SWOG 1500	66	26	61	14	93	7	18	0
TIVO-1	59 | 59	30	65	5	80	20	23 | 20	100
TIVO-3	62 | 63	21	61	18	0	100	NR	100
VEG105192	59 | 60	39	54	3	53	47	28 | 26	100

Abbreviations: NR, not reported

* where results were available by arm the figures are shown separated by a bar (|).

¤ In some cases these do not add up to 100% due to rounding and IDMC status not having been reported for a small proportion of patients

4.4. Ongoing studies

Six relevant ongoing studies were identified prior to receipt of company data, including two from the trial registries search. These were:

- NCT05012371, which compares lenvatinib and everolimus in combination against cabozantinib in a second or third line context after progression on a PD-1/PD-L1 checkpoint inhibitor[82];
- SUNNIFORECAST, which compares nivolumab and ipilimumab in combination against standard of care in a first line context in advanced non-clear cell RCC[83];
- A Study to Compare Treatments for a Type of Kidney Cancer Called TFE/Translocation Renal Cell Carcinoma (tRCC), which compares axitinib and nivolumab in combination against nivolumab and against axitinib in a population with multiple lines[84];
- Cabozantinib or Sunitinib Malate in Treating Participants With Metastatic Variant Histology Renal Cell Carcinoma, comparing each treatment in a population with multiple lines. [85]
- REFINE, which is investgating an extended schedule for nivolumab following nivolumab plus ipilimumab (8 weekly rather than 4 weekly) and is expected to produce results in 2025[86]
- A Study of Subcutaneous Nivolumab Monotherapy which is expected to complete in March 2025[87]

Three of these studies focus on the effectiveness of treatments in people with non-clear cell histologies. The NCT05012371 study is due to complete in April 2023 and is expected to provide highly relevant information on the comparative effectiveness of two treatments available for a previously treated population including data on their effectiveness after progression on a PD-1/PD-L1 checkpoint inhibitor, which is current standard practice. Unfortunately, however, this is a relatively small Phase 2 study (estimated enrollment of 90 participants). The other two studies looking at the mode and frequency of administration of nivolumab and could have a significant impact on the cost and cost-effectiveness of treatments for RCC when they report in 2025.

5. COST-EFFECTIVENESS MODEL DEVELOPMENT

5.1. Published cost-effectiveness studies

5.1.1. Search strategies

Systematic searches of the health economic literature were undertaken to identify 1) economic evaluations of relevant interventions and comparators, 2) studies reporting quality of life data in the form of utilities, and 3) UK cost and resource use studies. Search strategies are provided in Appendix 1.

Search strategies were developed by an information specialist and the final strategies were peer reviewed by another information specialist within our team. The search strategies used relevant search terms, comprising a combination of indexed keywords (e.g., Medical Subject Headings, MeSH) and free-text terms appearing in the titles and/or abstracts of database records and were adapted according to the configuration of each database. No publication status (published, unpublished, in-press, and in-progress) limits were applied.

Alongside the Medline and Embase searches detailed below, the following databases were searched to identify general economic studies: INAHTA, CEA registry, ScHCARRHUD, NHS EED, EQ-5D documents, and the NICE website. All were searched from 2009 (aligning with the publication of the first NICE appraisal in RCC) to 2023. We also search RePEc via EconPapers. Given the lack of an export functionality in EconPapers we reviewed the first 30 hits online. Finding no unique, in-scope citations among these 30, we added no documents from RePEc.

Abstracts and titles of references retrieved by the electronic searches were screened by two reviewers for relevance against the criteria specified in Table 7. Full paper copies of potentially relevant studies were then obtained and assessed for inclusion by two reviewers using the pre-specified inclusion/exclusion criteria. At both stages discrepancies will be resolved by discussion, with involvement of a third reviewer, where necessary. All duplicate papers were double checked and excluded.

Included studies were extracted by one reviewer into a bespoke database for each search. The quality of cost-effectiveness studies evaluating cabozantinib plus nivolumab was assessed using the Philips 2004 checklist for decision analytical models. [88]

Table 7: Inclusion and exclusion criteria for economic studies

PICOS item	Include	Exclude
Population	Studies of participants with advanced (stage 3 unresectable and stage 4) RCC	Studies of participants with early stage (not advanced) RCC
Intervention (economic evaluation searches only)	Cabozantinib plus nivolumab, pazopanib, tivozanib, sunitinib, cabozantinib, nivolumab plus ipilimumab, lenvatinib plus pembrolizumab, axitinib, lenvatinib plus everolimus, everolimus, nivolumab, avelumab plus axitinib*	Any other treatments not listed under inclusion Treatments used in the adjuvant setting
Comparator (economic evaluation searches only)	Any of the other interventions listed above (i.e. head-to-head studies) Usual care / physicians' choice / best supportive care	Any other treatments
Outcomes	**Economic evaluations** Incremental Cost Effectiveness Ratio expressed as cost per life year gained or cost per QALY Cost savings (cost-minimisation studies only) **Utility studies** Quality of life data expressed in the form of utilities regardless of the method of elicitation and valuation **Cost and resource use studies** Resource use data from UK studies Cost data from UK studies	Studies not reporting an included outcome
Study design	Economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost-minimisation) Systematic reviews of economic evaluations or utilities Conference abstracts will be included unless data are superseded by another conference abstract or full journal article	Abstracts with insufficient methodological details Editorials and commentaries
Data limits	Economic evaluations: 2009 Utility studies: 2009 Cost and resource use studies: 2017	

Abbreviations: QALY, quality-adjusted life year; RCC, renal cell carcinoma

Notes: * as belzutifan was included within the NICE draft scope it was included within the search terms for the searches conducted, these studies will, however, not be included during screening

5.1.1.1. Searches for economic evaluations

Searches for economic evaluations were carried out in Medline and Embase, using the SIGN economics filter. [38] The same terms were used for the economic evaluation searches as for the clinical RCT searches in respect of patient population and interventions. Searches were limited

to 2009 onwards, aligning with the publication of the first NICE appraisal in RCC. No limits by language were used.

Conference abstracts were included for the following conferences: American Association for Cancer Research, American Society of Clinical Oncology, American Urological Association, European Society for Medical Oncology, European Association of Urology, Genitourinary Cancers Symposium, International Conference on Translational Cancer Medicine and The International Society for Pharmacoeconomics and Outcomes Research.

5.1.1.2. Searches for health utilities

The utilities searches in Medline and Embase used the same population terms, but no intervention terms were used. Rather, population terms were combined with the CADTH utilities filter. [33] As with the economic evaluations search, searches were limited from 2009 onwards, and the same conferences were included as above. No language limits were imposed.

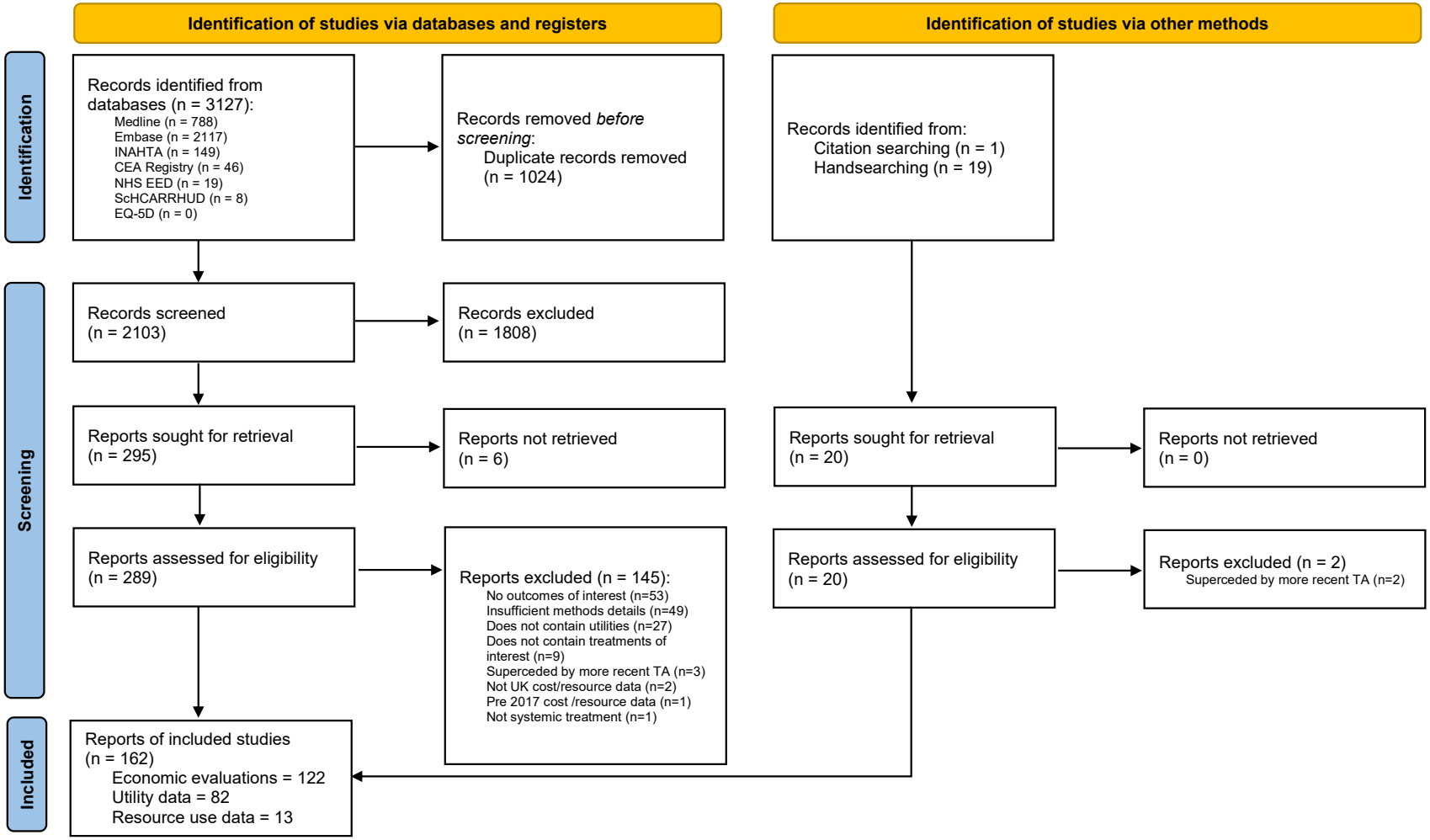
5.1.1.3. Searches for UK cost and resource use studies

UK cost and resource use searches in Medline and Embase combined patient population terms with the Cochrane cost of illness filter[89] and the NICE UK filter. [39] Studies were included from 2017 onwards, to ensure that only relevant data are found (aligning with the entry of immuno-oncology options into clinical practice post TA417[90]). Again, no language limits were imposed.

5.1.2. Results of the searches

In total, 162 papers were identified across the three searches (Figure 11). Some publications contained information relating to more than one review. 122 papers containing relevant economic evaluations were identified, 82 papers were identified containing utility data (discussed in Section 5.3.7) and 13 containing cost and resource use data (discussed in Section 5.3.8)

Figure 11: Economic literature review PRISMA



Abbreviations**:** INAHTA = International Network of Agencies for Health Technology Assessment; NHS EED = The NHS Economic Evaluation Database; ScHCARRHUD = School of Health and Related Research Health Utilities Database.

Note: a number of studies qualified for more than one of the economic reviews and therefore the total across each of the 3 reviews (122 + 82 + 13) sums to more than the number of reports included (n=162)

Of the 122 economic evaluations identified, the EAG has prioritised inclusion within this report prior to receipt of company data by initially looking at:

- Previous NICE technology appraisals from 2017 onward – 10 included
- Systematic reviews of cost-effectiveness studies from 2017 onward – 2 included
- Studies evaluating cabozantinib plus nivolumab – 7 included
- Sequencing models – 5 included
- Western (Europe, US, Canada, Australia and New Zealand) studies by recency of data – 15 included at this report stage

The data extraction grid that has been completed so far can be found in Appendix D.

5.1.2.1. Learnings from previous technology appraisals

Table 8 provides a summary of previous NICE technology appraisals in RCC.

The vast majority of previous NICE technology appraisals used a simple three-state partitioned survival (PartSA) model based upon progression status. This aligns with company preferences for oncology modelling as discussed in TSD 19.[91] The use of this structure may not, however, have been ideal as within a number of these appraisals (TA780,[92] TA650,[93] TA645,[94] TA512,[95] TA417[90]) the Committee raised concerns around the way that subsequent therapy was accounted for, expressing a clear preference that costs and effectiveness of subsequent lines should match and that Committee preference is to use UK data for both. This type of analysis would be very difficult to achieve in a PartSA model without access to patient level data for all involved treatments to allow statistical adjustment of OS. Within a state transition model, although evidence gaps will still remain, there is the flexibility to test the impact of different assumptions rather than having unquantifiable, and sometimes unacknowledged, uncertainty relating to the mismatch between subsequent treatments within trials and practice and the impact of this on effectiveness.

Another issue identified within previous appraisals relates to inconsistency in the evidence base. Different trial arms have been used to represent the reference treatment across appraisals and previous appraisals generally used HRQoL from the trial for the treatment currently being appraised. There are therefore different estimates of baseline risk for progression, death and HRQoL being used for the same population and same treatment across appraisals.

The EAG also note that the evolution of appraisals within RCC and lack of use of a common model and set of comparators has already led to some potentially counterintuitive decisions. Specifically, TA780[92] (a CDF re-review) did not compare nivolumab plus ipilimumab to cabozantinib (the only other option available specifically for intermediate and poor risk disease) as it was not in scope of the original appraisal in line with standard process at the time. TA858[19] then found nivolumab plus ipilimumab not to be cost-effective versus cabozantinib with pembrolizumab plus lenvatinib recommended on the basis of cost-effectiveness versus nivolumab plus ipilimumab and not cabozantinib due to high levels of usage of nivolumab plus ipilimumab in practice.

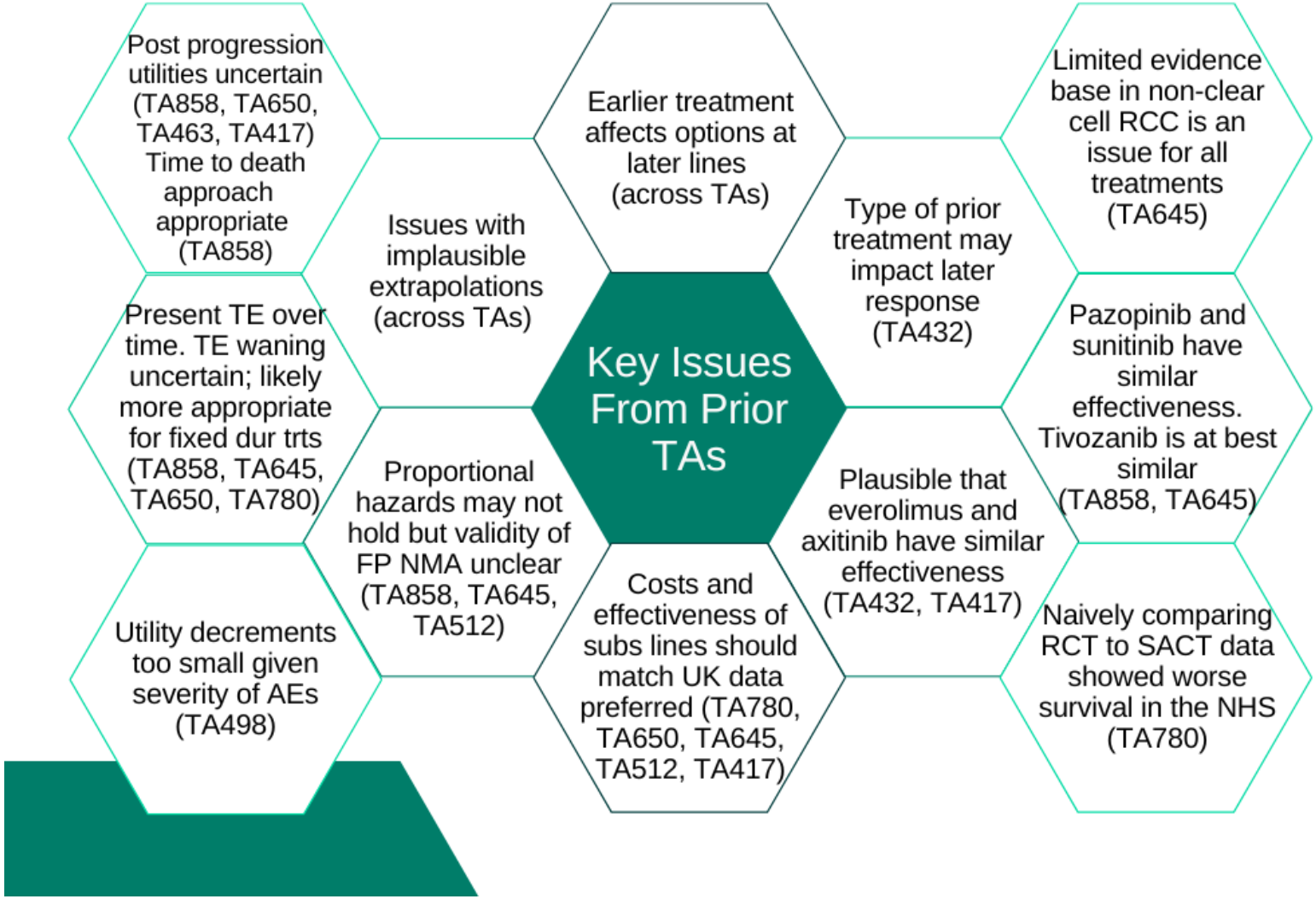
Table 8: Summary of previous technology appraisals

TA	Year	Recommendation population	Model type	Intervention	Comparators in final analysis	Source of HRQoL data	Committee ICER
TA858 (MTA) [19]	2023	1L int/poor risk, where nivolumab plus ipilimumab would otherwise be offered	3 state PartSA	Lenvatinib plus pembrolizumab	Int/poor risk: cabozantinib, nivo + ipi Favourable risk: sunitinib, pazopanib, tivozanib	KEYNOTE-581	EAG vs nivo + ipi = £133,362 vs cabo = £166,249 (list price analyses) Not c/e vs cabozantinib
TA830[21]	2022	Adjuvant: increased risk of recurrence after nephrectomy	State transition: DF, LR, DM and death	Pembrolizumab	Routine surveillance	KEYNOTE-426 for advanced RCC	N/A
TA780[92] (CDF review of TA581)	2022	1L int/poor risk	6 state PartSA (prog and tx states, terminal care, death)	Nivolumab plus ipilimumab	Sunitinib, pazopanib	CheckMate 214	vs suni = £25,897 - £36,041 vs pazo = £24,653 - £34,132
TA650[93]	2020	1L (not recommended)	3 state PartSA	Pembrolizumab plus axitinib	Pazopanib, sunitinib, tivozanib, cabozantinib (int/poor risk)	KEYNOTE426	vs suni = £59,292 - £76,972 vs cabo = £29,835 - £38,346
TA645[94]	2020	1L	3 state PartSA	Avelumab plus axitinib	Pazopanib, sunitinib, tivozanib, cabozantinib (int/poor risk)	JAVELIN Renal 101	Company: vs suni = £26,242 vs pazo = £29,542 vs tivo = £9,220 vs cabo = Dominant
TA542[96]	2018	1L int/poor risk	3 state PartSA	Cabozantinib	Sunitinib, pazopanib	TA512	vs suni = £37,793 vs pazo= £48,451 vs suni = £31,538
TA512[95]	2018	1L	3 state PartSA	Tivozanib	Sunitinib, pazopanib	TIVO-1 trial	Pazo dominates tivozanib & sunitinib
TA498[97]	2018	1 prior VEGF, ECOG 0-1	3 state PartSA	Lenvatinib plus everolimus	Axitinib, cabozantinib, everolimus, nivolumab	AXIS	Company: vs axi = £32,906 vs cabo = £16,083 vs nivo = £17,146 vs evero = £96,403

TA	Year	Recommendation population	Model type	Intervention	Comparators in final analysis	Source of HRQoL data	Committee ICER
TA463[98]	2017	Prior VEGF	3 state PartSA	Cabozantinib	Axitinib, nivolumab	METEOR and AXIS	Redacted
TA432[99]	2017	Prior VEGF	State transition 4 states: stable disease (no AEs), stable disease (AEs), prog and death	Everolimus	BSC, axitinib - exploratory analysis	Swinburn et al., (2010)	vs BSC = £51,700 - £52,261 vs axi = Dominant (list price)

Abbreviations: AE, adverse event; BSC, best supportive care; CDF, Cancer Drugs Fund; DF, disease free; DM, distant metastases; EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; ICER, incremental cost effectiveness ratio; int/poor, intermediate / poor risk using IMDC criteria; LR, loco-regional recurrence; MTA, multiple technology appraisal; prog, progression; PartSA, partitioned survival analysis; tx, treatment; VEGF; vascular endothelial growth factor; vs, versus; 1L, first line

Figure 12: Summary of issues from prior NICE appraisals of technologies for RCC



Abbreviations: AE, adverse event; FP NMA, fractional polynomial network meta-analysis; RCC, renal cell carcinoma; RCT, randomised controlled trial; SACT, systematic anti-cancer therapy dataset; TA, technology appraisal; TE, treatment effect

Figure 14 provides a summary of the key issues raised in prior NICE technology appraisals of technologies for RCC. Many of these are interlinked and stem from difficulties with the evidence base available in terms of maturity of information for extrapolation, quality of data for more historic treatments, lack of data in risk status subgroups, lack of data for non-clear cell histologies and methodological disagreements over the most appropriate way to handle violation of proportional hazards within trials.

The importance of subsequent therapy is highlighted in that earlier treatment affects options at later lines, as discussed in Section 25, and that there is some evidence that type of prior treatment may impact outcomes at later lines. It is clear from a number of prior TAs that Committee preference is for cost and effectiveness to match when considering subsequent treatments and for UK patterns of subsequent therapy to be used above trial data.

It is also clear that there are limitations to the available HRQoL data in RCC, in particular difficulties capturing the full impact of issues with tolerability for certain treatments and uncertainty around post progression utilities (a wide range of estimates are available which is likely influenced by changing practice around subsequent treatment and by collection of post progression utilities being limited to 30 days in a number of the trials).

Lastly, appraisals that have included UK RWE have shown worse outcomes in NHS practice than in trials, based on naïve comparison. There was some suggestion that this may be due to a higher proportion of patients having intermediate / poor risk status in practice than may be included in some trials.

5.1.2.2. Learnings from systematic reviews

Two systematic reviews of the cost-effectiveness of treatments for RCC were identified. [100,101] Both considered only the cost-effectiveness of immune checkpoint inhibitors.

Verma (2018) [100] identified three studies considering the cost-effectiveness of nivolumab versus everolimus for previously treated RCC[102-104]: two PartSA models with considerable differences in results (ICERs of $51,714 per QALY [pharma sponsored] and $146,532 per QALY) and driven by differences in extrapolation techniques, and a state transition model that reported a similar ICER versus everolimus to the more conservative of the PartSA approaches, but concluded that nivolumab was not cost-effective versus placebo. Uncertainties were raised in the review around optimal dosing and duration of immune checkpoint inhibitors and the impact of late presenting toxicities.

Philip (2021) [101] identified 23 studies published between 2008 and 2020, across 9 different countries (first-line treatment (n = 13), second-line treatment (n = 8), and first-line and beyond (n = 2)). The majority, fourteen studies, included the use of novel immune checkpoint inhibitors nivolumab, ipilimumab, pembrolizumab), half of which found that checkpoint inhibitors were more cost-effective when compared to oral systemic therapies (sunitinib, everolimus, axitinib, pazopanib, and cabozantinib). The review did not identify any studies of cabozantinib plus nivolumab and did not look in detail at the drivers of results.

5.1.2.3. Learnings from economic evaluations of cabozantinib plus nivolumab

Seven publications reported an economic evaluation of cabozantinib plus nivolumab (Table 9). [105-112] All of the publications used data from CheckMate 9ER (with the majority using the March 2020 database lock). The four papers not sponsored by industry compared to sunitinib. The other three compared to a variety of treatments including TKIs and combination therapies.

All five publications not sponsored by Ipsen, including the abstract sponsored by Bristol Myers Squibb (BMS), concluded that treatment was not cost-effective based upon the stated prices. BMS concluded that their wholly owned combination (nivolumab plus ipilimumab) dominated when compared to cabozantinib. Conversely, Ipsen concluded in their two analyses that when comparing cabozantinib plus nivolumab to nivolumab plus ipilimumab, that QALY gains were either the same or the opposite direction (i.e. favouring cabozantinib plus nivolumab). The rationale for these differences is unclear.

None of the publications were conducted from a UK perspective and none were high quality, with survival extrapolation methods either unclear or driven only by visual and statistical fit. Quality assessment was conducted using the Phillips checklist and is included in Appendix D.

One study explored the difference a state transition vs a PartSA model structure made upon outcomes and concluded that there was little difference. Drug costs, quality of life and effectiveness inputs were key drivers in the majority of models with relative dosing intensity (RDI) also being a key driver in one. The utility sources used by the authors of the papers that were not industry funded were acknowledged as not ideal as EQ-5D data from CheckMate 9ER was not available to them.

Table 9: Summary of published economic evaluations of cabozantinib plus nivolumab

	Li 2021	**Liao 2021**	**Liu 2022**	**Marciniak 2022**
Analysis country	US	US	US	France
Funder	US government	Chinese government	Chinese government	Ipsen
Price year	2021	2021	2021	Unclear
Time horizon	Lifetime	Lifetime	10 years	50 years
Comparators	Sunitinib	Sunitinib	Sunitinib	TKIs[+] **and c**ombinations[¥]
Model structure	DES based on PFS, discontinuation & mortality due to AEs, lifetables and OS during BSC Curve selection not justified	3 state PartSA Extrapolation methods unclear	3 state models: state transition & PartSA Curve selection statistical and visual fit only	3 state PartSA Curve selection statistical fit only
Source of efficacy data	CheckMate 9ER (March 2020 DBL), AXIS, TIVO-3, dovitinib vs sorafenib RCT[28,54,69,74]	CheckMate 9ER (March 2020 DBL) [28]	CheckMate 9ER (March 2020 DBL) [28]	CheckMate 9ER[28] (Sept 2020 DBL) NMA for comparators
Price of cabo 60mg / nivo 240mg	$491.30 / $6,849.84 (average CMS sale price)	$866.51 / $8,015.04 (Red Book)	$515 / $7,432 (average CMS sale price)	Not reported
Utilities	By line 0.82, 0.77, 0.66, and 0.494 -0.157 for Grade 3+ AEs	PFS cabo + nivo 0.848, PFS sunitinib 0.73, progressed 0.66	PFS cabo + nivo 0.75, PFS sunitinib 0.73, progressed 0.66	Not reported
Utility sources	Cella 2018 (METEOR) [113] De Groot 2018 (PERCEPTION) [114] Wan 2019 (CheckMate 214) [115] Patel 2021 (myeloma) [116] Wu 2018 (VEG105192 trial) [75] Selection methods unclear	Wan 2017[104] Wan 2019[117] Wu 2018[118] Data not from CheckMate 9ER. Selection methods unclear	Cabo + nivo estimated from FKSI Wan 2019[115]	CheckMate 9ER
Subs therapy	Axitinib → sorafenib → BSC	Unclear, average cost	CheckMate 9ER	Taken from individual publications for 1L therapies, includes treatments not available in the UK
Perspective	Payer	Payer	Payer	Not reported but appears to be payer
Base case ICER	$508,987/QALY	$863,720/QALY	$555,663/QALY vs $531,748/QALY*	Uses placeholder costs for some inputs 7.4 life years, 5.4 QALYs for both nivo/ipi and nivo/cabo Life-year range, 5.1–6.2; QALY range, 3.8–4.6 for TKIs

				Life-year range, 6.3–7.1; QALY range, 4.7–5.2 for other combinations
Key drivers	Patients age at treatment, first line utility, cost of nivo	PF utility, cost of cabo, effectiveness parameters	PF utility, drug costs	Not reported

	Tempelaar 2022	**Wang 2022**	**Yoshida 2022**
Analysis country	France	China	Brazil
Funder	BMS	Chinese government	Ipsen
Price year	2020	2022	Unclear
Time horizon	15 years	20 years	Unclear
Comparators	Nivo/ipi, pembro/axi, pazo, suni	Sunitinib	Ipi/nivo, pazo, suni
Model structure	3 state PartSA Extrapolation methods unclear	3 state PartSA Curve selection statistical and visual fit only	3 state PartSA Extrapolation methods unclear
Source of efficacy data	CheckMate 9ER Multi-dimensional treatment effect NMA vs sunitinib	CheckMate 9ER (March 2020 DBL)	CheckMate 9ER[28] (datacut unclear) NMA for comparators
Price of cabo 60mg / nivo 240mg	Not reported	$491.20 / $3,482.57	Not reported
Utilities	Not reported	PFS cabo + nivo 0.848, PFS sunitinib 0.73, progressed 0.66 -0.157 for Grade 3+ AEs	Not reported
Utility sources	CheckMate 9ER French value set	Li 2021, Liao 2021	CheckMate 9ER
Subs therapy	Not reported	CheckMate 9ER	Clinical studies, source and data not reported
Perspective	All payer	Health system	Not reported
Base case ICER	Cost-efficiency frontier was only comprised of two treatments: pazopanib and nivo/ipi. Nivo/ipi strictly dominated nivo/cabo (incremental Euros / incremental QALYs: 63,792/-0.221)	$292,945/QALY	vs suni BRL 365,591/QALY vs pazo BRL402,944/QALY vs nivo/ipi BRL347,698/QALY (int/high risk)
Key drivers	Multi-dimensional treatment effect NMAs	Drug costs, utilities at progression, subsequent treatment	RDI, discount rate, drug costs

Notes: * state transition vs PartSA; ⁺TKIs included: cabo, pazo, temsirolimus, tivo, sorafenib, suni; ¥ combinations: ipi/nivo, axi/ave, axi/pembro, lenva/pembro

Abbreviations: AE, adverse event; BRL, Brazilian Real; BSC, best supportive care; CMS, Centers for Medicare and Medicaid Services; DBL, database lock; DES, discrete event simulation; FKSI, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index; ICER, incremental cost effectiveness ratio; OS, overall survival; PF, progression free; PFS, progression-free survival; PartSA, partitioned survival analysis; QALY, quality-adjusted life-year; RDI, relative dosing intensity; US, United States

5.1.2.4. Learnings from previous sequencing models

Five publications were identified that provided information on three models considering sequencing within RCC. One model looked specifically at patients assessed as IMDC intermediate / poor risk. All of the models were discrete event simulation analyses (two papers discussed what appeared to be the same model using the DICE framework[119,120]). Model structures varied with the more complex manufacturing led models including response, TTD, reason for discontinuation (AE or progression), TTP or next treatment, adverse events and death and the academic-led model considering only treatment line, adverse events and death.

One of the studies used data collected retrospectively from a patient registry, [121] in the Netherlands the others used trial data supplemented by network meta-analysis. None of the studies considered the full network included in this analysis, none report a UK perspective and none considered sequencing after cabozantinib plus nivolumab. Key considerations within the publications include:

- **Access to patient level data**: the majority of the models were produced with industry sponsorship and included analysis of patient level data from manufacturer sponsored trials. This was necessary to produce the required risk equations accounting for the impact of population characteristics and prior treatments on prognosis. Where data was not available, information from treatments with a similar mechanism of action was generally substituted
- **Issues with reporting of time to treatment discontinuation and time to receipt of subsequent treatments** meaning that assumptions were required (e.g. assumption of similar relative effectiveness to PFS or assumption that TTD and TTP are equal)
- **Difficulties in matching observed treatment effects for subsequent treatments** in the CheckMate 214 trial with data observed in clinical trials for subsequent therapies
- Analysis based on CheckMate 025 **assumed that the efficacy of second-line treatment was not affected by the first-line agent** received (due to the first-line options modelled being only TKI monotherapy)
- The need to **include non-RCC mortality separately,** as trial-based mortality hazards were often decreasing at the end of trials

- The **potential for a treatment free interval** for patients receiving immuno-oncology treatments in the first line setting (demonstrated in a proportion of participants in CheckMate 214)
- Difficulties using standardly assessed progression to determine treatment failure on immuno-oncology due to the potential for **'pseudo-progression'**; a well-recognised phenomena that has been discussed in multiple NICE TAs, and fitting curves to PFS due to initial **drops in the KM curve linked to scanning protocols**
- **Limitation in the number of lines of treatments explicitly modelled** (maximum of 2 active treatments)
- **Differences between real-world treatment practice and best practice** as detailed within guidelines. In de Groot 2017[121] only 54% of the patients received a targeted therapy; one in four fulfilling eligibility criteria did not receive targeted therapy

Key prognostic factors identified within a number of analyses included:

- Risk score (MSKCC)
- Age – relatively small impact
- Region (US vs Canada/West Europe/North Europe vs rest of world) – inconsistent direction of effect
- Race – inconsistent direction of effect
- Performance status (KPS, WHO, ECOG) – higher is poorer prognosis
- Histology – non-clear cell poorer prognosis
- Prior nephrectomy – improved prognosis
- Site of metastases – liver and lung metastasis poorer prognosis
- Number of lesions – more is poorer prognosis
- Laboratory values (abnormal values poorer prognosis); LDH, Alkaline phosphatase, haemoglobin, neutrophil count, albumin

- PD-L1 status (poorer prognosis for TKIs, not predictive for immuno-oncology in CheckMate 214)

5.1.2.5. Learnings from other published economic evaluations

Data was extracted from 15 additional studies. 8/15 (53.3%) of the studies examined first line therapies, 6/15 (40%) examined second line therapies, and one study assessed treatments for both first and second line. All were based in North America, Europe, Australia or the UK, one of which (Sarfaty et al, 2017) was included in an included literature review (Verma et al, 2018). All studies either evaluated patients with poor/intermediate risk status (IMDC) or did not report the risk status. All of the model structures used in these studies have been used by a previous NICE TA, literature review, or a sequencing model. The model structures used have been summarised in Figure 13 and Figure 14. All clinical effectiveness and utility inputs were derived from trials, or from previous NICE TAs.

Figure 13: Model structure, published economic evaluations

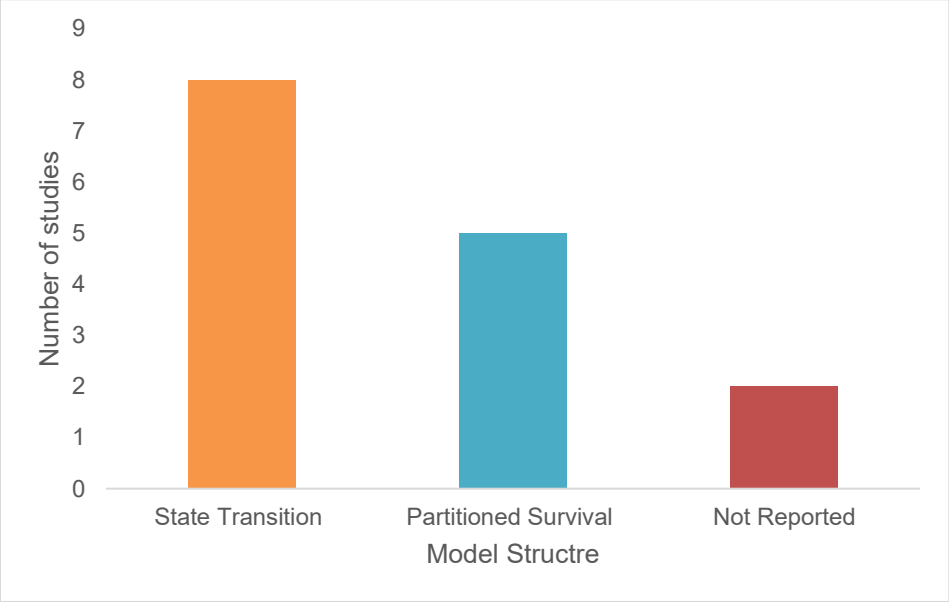
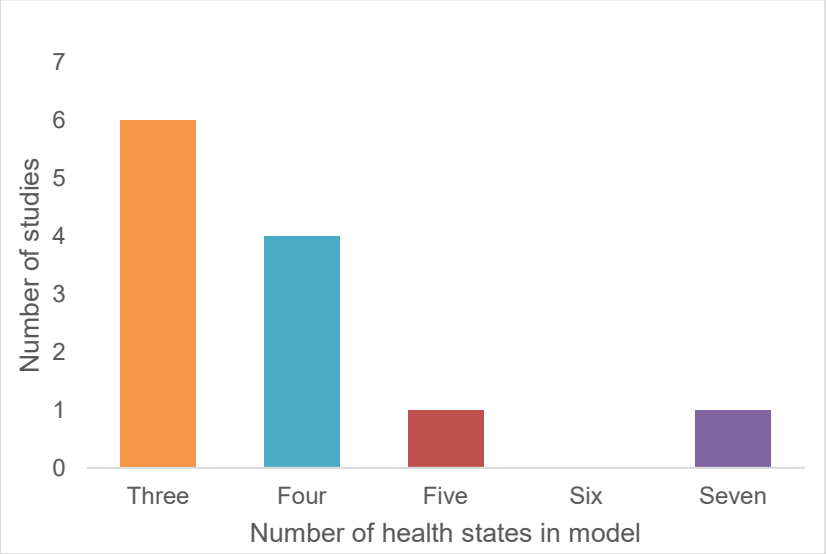


Figure 14: Number of health states used, published economic evaluations



Note: 3 studies did not report the number of health states modelled

Models that incorporated only three states included pre-progression, post-progression and death. For those with four states, the additional health state was progression to second line treatment and progression to BSC, or they were not reported in the study. The study including five states included pre and post progression on and off treatments, and death, and the study with seven health states included pre-progression (no treatment), pre-progression (treatment), pre-progression (dose reduction), unobserved progression, progression detected by CT scan, death from other causes, death from RCC.

Across all reviewed first-line studies, nivolumab plus ipilimumab resulted in the highest QALY gains over comparator treatments, including pembrolizumab plus axitinib, nivolumab plus cabozantinib as well as monotherapies sunitinib, pazopanib and cabozantinib. Cabozantinib resulted in a higher QALY gain compared to sunitinib, which subsequently had a higher QALY gain than pazopanib. Pembrolizumab plus axitinib led to more life years gained than sunitinib, and in second line, nivolumab resulted in a higher QALY gain than everolimus.

There were no additional learnings relevant to the specification of the model for the pathways pilot identified in the papers reviewed so far.

5.2. Planned expert elicitation

5.2.1. Rationale for planned structured expert elicitation

The maximum follow-up available within the available clinical trials identified is just over seven years (CheckMate 025[122]). A median of 32.9 months of data are available for CheckMate 9ER, with the median OS only just reached for cabozantinib plus nivolumab within published evidence identified so far. [123] Whilst this is relatively long when compared to the length of follow-up usually available within a NICE technology appraisal, this is nevertheless still short when compared to model time horizons of 40 years in the more recent published examples for first line treatments. Given this and the fact that recent changes to the treatment pathway are expected to impact on outcomes we plan to conduct a structured expert elicitation exercise to inform expected long-term survival (see Section 5.2.5).

Materials from the STEER repository[124,125] which was developed in line with the Medical Research Council (MRC) protocol, [124] will be used to plan and conduct this exercise.

5.2.2. Quantities of interest

We will seek to understand the expected OS outcomes for the subsequent therapy mix in CheckMate 9ER, the impact of different types of first line treatment and the impact of different sequence lengths for subsequent treatment.

There are two potential methods to elicit the required information, either:

- landmark survival estimates for treatment sequences
- landmark estimates of either PFS or TTNT per line of therapy

We will take expert input on which of these is more intuitive. Given the second option involves more questions, we have initially proposed to implement the first option. Sequences have been selected to reflect the CheckMate 9ER trial and provide information on sequences viewed as best practice / most commonly used in the UK. As data are still being gathered on UK treatment pathways these are therefore subject to change.

Data will be elicited for no more than 10 sequences or treatments to keep the exercise manageable.

Favourable risk group:

- Cabozantinib plus nivolumab followed by the subsequent therapy mix in CheckMate 9ER
- Sunitinib followed by the subsequent therapy mix in CheckMate 9ER
- Sunitinib → lenvatinib plus everolimus → nivolumab → cabozantinib → BSC

Intermediate / poor risk group:

- Cabozantinib plus nivolumab followed by the subsequent therapy mix in CheckMate 9ER
- Sunitinib followed by the subsequent therapy mix in CheckMate 9ER
- Nivolumab plus ipilimumab → sunitinib → lenvatinib plus everolimus → cabozantinib → BSC
- Pembrolizumab plus lenvatinib → cabozantinib → everolimus → BSC
- Sunitinib → lenvatinib plus everolimus → nivolumab → cabozantinib → BSC
- Sunitinib → lenvatinib plus everolimus → nivolumab → BSC
- Sunitinib → lenvatinib plus everolimus → BSC

Clinicians will be provided with the demographics of the population to be estimated to reduce the potential for variation driven by patient characteristics. We plan to match this to the expected UK patient population eligible for first-line treatment rather than to CheckMate 9ER.

Clinicians will be asked to estimate landmark survival at three timepoints for each sequence:

- 5 years
- 10 years
- 20 years

Two additional questions on the expected impact of use of adjuvant pembrolizumab per NHS guidance on overall survival in the advanced setting may be added. These questions would be expected to be asked as a modification of the landmark estimates for the CheckMate 9ER sequences in the intermediate / poor risk group to account for people who have received prior

adjuvant pembrolizumab. The level of uptake of adjuvant pembrolizumab in UK practice will drive whether or not these questions need to be asked.

5.2.3. Accounting for dependence between variables

A number of the quantities of interest are dependent upon others. Outcomes at one time point are dependent upon another. Where this is the case, dependent variables will be expressed in terms of independent variables.

Wording will be formatted in as clear a manner as possible and will be piloted with one clinician. An example of potential wording might be:

" What proportion of patients will be alive at five years for the patient population described in the pack if they received the following treatment sequence: sunitinib → lenvatinib plus everolimus → nivolumab → cabozantinib → BSC"

" Of those patients who were alive at five years, what proportion would you expect to remain alive at ten years for the patient population described in the pack if they received the following treatment sequence: sunitinib → lenvatinib plus everolimus → nivolumab → cabozantinib → BSC"

There are, however, less clear-cut cases where eliciting a relative effect may be beneficial e.g. outcomes with adjuvant pembrolizumab before treatment are expected to be expressed in a dependent manner and outcomes for the same sequence for a different risk status. We will assess whether a constant relative effect is reasonable based upon clinical advice and available datasets to determine how these cases will be handled.

5.2.4. Expert recruitment

We will seek to recruit a minimum of five and a maximum of ten oncologists who we would expect to be the experts most likely to be able to provide input on expected survival for given treatment sequences. We will seek to include experts from centres from a mix of geographies across England and from a mix of types of centres: e.g. academic vs clinical, urban vs rural populations. Experts will be identified by hand searching RCC publications and NHS websites. Recruitment will be focussed on substantive skills as recommended within the MRC protocol rather than normative skills. Conflicts of interest will be minimised where possible; experts will be required to declare any potential conflicts as consistent with NICE policy.

The planned inclusion criteria for experts are:

- Willing and able to participate within the required timeframe
- Absence of specific personal and financial conflicts of interest
- Published within the field of advanced RCC or referred by another included expert
- At least five years of experience treating people with advanced RCC

5.2.5. Approach to elicitation

Given the timeframe available, the following approach is proposed to seek quantitative expert input:

- Background materials to be sent to experts including a summary of existing trial and observational data
- One-to-one or group meeting to introduce the exercise and provide training; training to be adapted from the PowerPoint slides provided within the STEER tools
- Online survey to be sent to experts for remote individual completion using the roulette method of the STEER R tool . The tool includes:
    - Elicitation of plausible upper and lower limits (95% CI) as an initial step
    - Elicitation of values using the roulette method
    - Feedback of values for expert revision and request for provision of rationale and comment
- Check of responses and follow-up queries sent if any responses are unclear or inconsistent
- Distributions to be fitted to individual expert elicited judgements – the statistical best fit distribution will be selected from the normal, gamma, log normal and beta distributions
- Mathematical aggregation via linear opinion pooling

There is a lack of empirical evidence on whether fixed interval methods (such as the roulette method) or variable interval methods work better for healthcare decision making, and both methods have been used in this context. [124] Fixed interval methods are generally preferred by

experts and are more intuitive, but there may be a tendency for experts to focus on the shape of the histogram rather than the probabilities they are expressing. Given the timeframe of this work and the number of quantities of interest necessitates conducting the elicitation via remote survey the roulette method was preferred as the benefit of increased intuitiveness was considered to outweigh the potential issues with focus.

There is also a lack of empirical evidence to inform a preferred method to fit distributions, [124] therefore we propose to use the statistical best fit. We will test four commonly used distributions and if the fitted distribution causes substantial variation in estimates we will test alternatives in sensitivity analysis.

The MRC protocol advises the use of linear pooling with equal weights for mathematical aggregation for simplicity and due to a lack of research on how to generate appropriate weights. [124]

5.3. EAG economic analysis

5.3.1. Model structure

A *de novo* decision model was constructed for this appraisal. Adaptation of previous models, including the model used within the TA858 MTA, was not possible as these were not accessible for such use and also due to differences in the scope of this and previous appraisals.

The following factors were considered when determining the model structure to be used:

- The nature of the disease
- The need to be able to look at multiple decision nodes within the treatment pathway
- The key issues identified within the review of previous economic analysis and NICE technology appraisals
- Methodological guidance
- The available data (type, format and coverage)
- Timelines

5.3.1.1. Nature of the disease

The goal of treatment for RCC is to extend life and delay progression; with long-term survival considered a reasonable goal in the context of many active agents. [126,127]

People may go through multiple lines of treatment. Experts consulted in the scoping meeting for this appraisal recommended that a maximum of four lines of treatment followed by BSC should be incorporated in the model. A previous UK audit found that on progression 69% of patients were able to receive second-line therapy, 34% were able to receive third-line therapy, 6% were able to receive fourth-line therapy and only 1% received a fifth. [128]

An analysis of 10,065 patients across 19 RCTs found a good correlation between OS and PFS for targeted agents and immuno-oncology treatments. [129] An analysis of real-world data including 171 patients with metastatic RCC found good correlation between both PFS and TTNT and OS (Spearman's correlation coefficients of 0.70 and 0.68 respectively). [130] TTD, was however, less well correlated with OS (Spearman's correlation coefficient of 0.56). Clinical expert advice to the EAG was that TTNT and PFS were well correlated and that TTNT was a reasonable proxy for PFS. Additional information on surrogacy between endpoints is expected to be added following receipt of company and observational datasets.

Improving HRQoL by relieving symptoms and tumour burden is also an important clinical outcome for people with RCC. [126] Quality of life is impacted by both the stage of the disease and treatment received. Experts consulted indicated that TKI toxicities can have considerable impact on quality of life, particularly as people cannot take prolonged treatment breaks. Within the scoping workshop for this appraisal, experts noted these include chronic fatigue, chronic diarrhoea and hand / foot syndrome. With immuno-oncology treatments, immune-related adverse events are rare but can be serious in nature.

In addition to the impact on the patient, HRQoL is predictive of mortality in RCC; particularly non-RCC-specific mortality, [131] along with other well recognised factors such as age and sex.

Treatment durations vary. Treatment is either given until progression or unacceptable toxicity, or for some immuno-oncology treatments, stopping rules are in place such that treatment is only given for a fixed length of time (typically 2 years).

Given this model is conceptualised entirely using a disease-oriented approach, as recommended by TSD 13, [91] it would consist of health states based upon:

- Length of life
- Disease status; whether or not the patient has progressed on their current line of treatment and what line of treatment they are receiving (which may be a reasonable proxy for progression)
- Type of treatment received and whether the patient is on or off treatment

Patient characteristics which are likely to impact upon length, and quality of life, such as age, sex and risk status should also be considered as necessary. In the case of a cohort model, it is necessary to ensure that the patient cohort modelled is reflective of UK practice and that changes in quality of life and mortality risk attributable to the aging process rather than the disease are captured.

5.3.1.2. Available data

As discussed in Section 4.2.2.4, all identified RCTs provided information on OS and PFS endpoints and 14 of 24 trials reported HRQoL data. No trials reported data for TTNT treatment, only two reported data on TTP and relatively few reported TTD. Data for risk subgroups is less complete than for the overall population, with gaps likely to be more of an issue in the favourable risk population. Anonymised IPD was requested by EAG for CheckMate 9ER but could not be provided. TTP data has been requested along with information on TTNT from CheckMate 9ER and is expected to be provided. Data from previous modelling exercises conducted within prior NICE appraisals is also not available to the EAG for model input.

RWE is still being identified; however, it is expected based upon current information that the following types of data may be available:

- Anonymised IPD for a UK population from a selection of centres including PFS, time on treatment, line of treatment, risk status and other population characteristics
- Aggregate data for a UK population from a selection of centres including on treatment, line of treatment and basic population characteristics

It should be noted that PFS as measured within trials and PFS as measured in practice can differ substantially as patients are not routinely scanned as frequently in practice as in trials.[132,133] This can lead to seemingly perverse results where PFS in the real-world is longer than in

trials, but OS is shorter. The feasibility of implementing methods to account for this within this appraisal will depend upon when data are received and is under investigation.

5.3.1.3. Key issues identified within previous economic analysis

The developed model should be able to handle the following additional issues identified in prior economic analyses (Section 5.1.2):

- Matching costs and effectiveness for subsequent lines of treatment
- The potential for treatment effect waning
- Lack of clarity over the most appropriate approach to modelling quality of life (progression status vs time to death)

The first of these is the most relevant to determining the overarching model structure as, although the precedent for prior appraisals has been the use of a partitioned survival approach in most previous TAs, this structure cannot readily handle adjustment for a different subsequent therapy case mix where patient level data cannot be accessed to implement statistical analyses to adjust for treatment switching.

5.3.1.4. The need to be able to look at multiple decision points

In order to fulfil all of the objectives, the model needs to be able to start at a user-defined line of treatment for a user-defined population and include a user-defined list of therapies available at each line from then onwards. The type of treatment received in a prior line impacts on options available at later lines and may also impact outcomes.

This sort of problem naturally lends itself to a discrete event simulation (DES) model or a state transition structure. The sequencing models identified within the economic literature review were all discrete event simulation analyses.

TSD15 considers the key benefits of a patient-level simulation to be:

- The ability to model non-linearity with respect to heterogeneous patient characteristics
- The ability to determine patient flow by the time since the last event or history of previous events
- Avoiding limitations associated with using a discrete time interval

- Flexibility for future analyses, particularly when compared to models implemented in Excel
- The ability to model interactions - not relevant to this decision problem
- Potential for efficiency savings within probabilistic sensitivity analysis (PSA)

As patient level data are not available to the EAG for any of the treatments involved in this decision problem, the ability to model non-linearity with respect to heterogeneous patient characteristics is of no additional benefit.

A DES would be more efficient for handling time-to-event outcomes for subsequent lines of treatment where an exponential curve fit is inappropriate, however, alternatives such as the use of tunnel states are available in a state transition structure. The limitations associated with a discrete time interval can be reduced through the use of a smaller time interval.

There are also disadvantages: there can be difficulties in interpretability due to the complex nature of such models and DES models are indeed an investment; they take additional time to build compared to simpler model structures. The timeframes available for this pilot do not lend themselves to the use of a DES. For example, the IVI-NSCLC simulation model took a year and a half to build. [2]

There are a limited number of examples of use of DES within prior oncology NICE technology appraisals[134-136] and only one the authors are aware of where the disease area endpoints were OS and PFS. [134] The drivers for this are likely a mixture of precedent, data availability to gain the benefits from additional flexibilities and issues with interpretability and level of complexity for reviewers.

For example, in the abiraterone appraisal (TA387), the company submitted a DES in order to allow more flexibility to reflect a sequence of treatments and to allow the modelling of response to treatments that depend on previous treatments, both highly relevant to this decision problem. The submitted model also benefited from the availability of patient level data allowing the modellers to account for patient characteristics that may impact on outcomes. The Committee, however, agreed that using a DES model was not unreasonable, but considered that the company's model was particularly complex. [137] The ERG considered that *"an individual patient simulation by means of a DES could have been avoided, since acknowledging patient heterogeneity does not necessarily require patient level simulation."* [138]

5.3.1.5. Methodological guidance

The most relevant TSDs to consider in determining the most suitable model structure(s) for this decision problem are TSD13, TSD15 and TSD19. [91,139,140] The application of TSD13 is discussed in Section 5.3.1.1 and the application of TSD15 is discussed in 5.3.1.4. Given the majority of prior appraisals used a partitioned survival approach and those that did not use this structure were state transition models, the recommendations provided in TSD19 were given careful consideration.

TSD19 recommends consideration is given to both theoretical and practical considerations in determining modelling approach. In this case assuming that PFS and OS are independent of each other, as is the case for a PartSA analysis, would be a considerable stretch to credibility given the nature of the disease and clinical advice received. Given the data identified so far for OS (Section 4.2.2.4), a substantial proportion of the modelled time horizon will use extrapolated data, median OS was only just reached for CheckMate 9ER within the most recently published data-cut for example. [123] As noted in TSD19: *"the lack of structural link between endpoints in PartSA models may increase the potential for inappropriate extrapolation."*

There are also limitations to the implementation of a state transition structure given the limited data available in the context of this appraisal which need acknowledging. As patient level data are not available to the EAG, a multi-state modelling approach such as that defined by Williams et al. cannot be implemented. [141] Limited data are available to define the split between progression and death events within PFS and what data are available does not provide information on the timing of events. Only two trials identified within the literature review reported data on TTP. This means that NMA is only possible for PFS as a whole at a given line of treatment rather than for individual transitions.

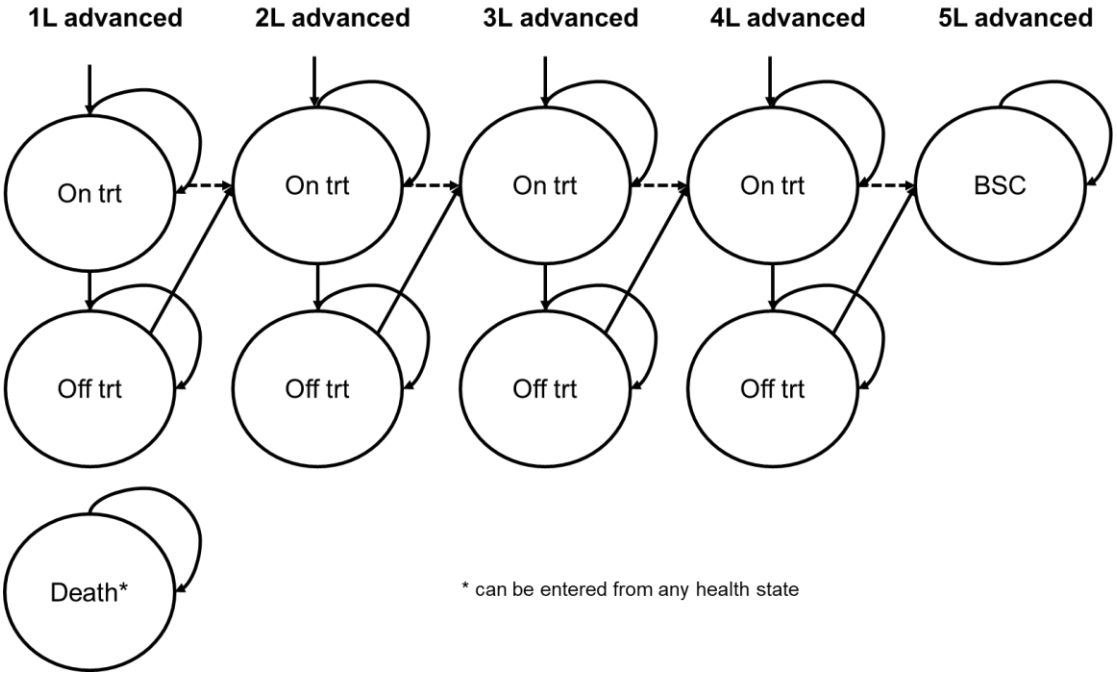
TSD19 recommends the presentation of results based upon a PartSA approach alongside those from a state transition model where a state transition structure is used given the need for further methods research.

5.3.1.6. EAG model structure

Figure 15 demonstrates the planned EAG model structure. The model is expected to allow for up to four active lines of treatment with patients who complete four lines moving to BSC. Patients will be able to receive BSC as a line of treatment at earlier lines, in this case patients will remain on BSC within that line until death.

Transitions between health states are envisioned to be driven by progression status in the model base. The option to allow the use of TTNT is being considered to make best use of data from RWE.

Figure 15: Model structure



Given the various considerations detailed above, the base case model structure is expected to be a hybrid of a partitioned survival and state transition approach based upon the approach used within TA798. [142] TTP and PFS data from CheckMate 9ER will be extrapolated and the difference between the two used to define pre-progression survival (Pre-PS). Treatment effects for other treatments will be applied from the NMA and will assume that the treatment effect across TTP and Pre-PS is the same. We refer to this hybrid simply as a state transition model throughout the report.

Data for time on treatment / time to treatment discontinuation (TTD) will also be taken from CheckMate 9ER and extrapolated. PFS data are expected to be used for the relative treatment effect for comparators here as well, given the lack of reported TTD data. Available data from trials which report TTD will be used to check that the relationship between TTD and PFS is similar to that within CheckMate 9ER in other trials where treatments are given until progression or unacceptable toxicity. Fixed duration treatments will be implemented based upon the maximum treatment duration and information on relative dosing intensity, where available.

Data for subsequent lines following progression on first-line treatment will be taken from available RWE and trial data for treatment effects at later lines of treatment with the proportion of patients receiving each type of treatment modelled to reflect UK practice within the base case analysis.

The structural assumptions made within the base case model are therefore expected to be:

- OS is dependent upon progression status and line of treatment; this implies surrogacy between PFS and OS, an assumption which appears to be supported by available literature
- OS is independent of whether or not a patient is on treatment within a particular line
- TTD and PFS are independent; the impact of this is expected to be limited and will be mitigated through selection of the same functional form for fitted curves
- TTP and PFS are independent; the impact of this is expected to be limited and will be mitigated through selection of the same functional form for fitted curves
- The treatment effect from the NMAs for PFS can be applied to TTP, Pre-PS and TTD endpoints
- Patients receive subsequent treatment on progression
- Transitions for first-line are dependent upon risk status, transitions for later line patients are not dependent upon risk status (given that in practice this is only measured at first-line)

The impact of the type of previous treatment on outcomes at later lines will be included where possible, however, the ability to do this is expected to be limited based upon data identified so far.

A PartSA will also be presented as recommended within TSD19. This model will assume by its nature that OS, PFS and TTD are independent and that any differences between the subsequent therapy mix in practice, CheckMate 9ER and other trials within the NMA do not impact either on relative effectiveness modelled. As such, an additional within trial comparative analysis of only cabozantinib plus nivolumab and sunitinib using CheckMate 9ER data alone will be produced where the impact of this assumption is tested.

Given the proposed primary model structure (state transition), calibration to expected OS estimates may be required.

5.3.1.7. Model implementation

The model will be implemented in R given the complexity of the future need to evaluate large numbers of treatment sequences, the need for the model to be reusable for future HTAs and the number of structural options required to be explored.

The use of R has a number of benefits including the integration of the conduct of the core statistical analysis (survival curve extrapolation) within the model. [143,144] Table 10 provides a comparison of the analytical capabilities of R and Excel from a published example using a side-by-side PartSA and state transition structure. The advantages to run time and analytical options are clearly demonstrate for the simpler decision problem addressed by that model (only one line of treatment).

Table 10: Comparative analytical capabilities between R and Excel models in oncology

Functionality	R model	Excel model
Live fitting of parametric models	All parametric models are fitted to the active dataset	Parametric models need to be fitted to the active dataset externally, and results copied into model—a laborious task for updates to data-cut or subgroup exploration
PartSA and StateTM modelling	Model includes PartSA and StateTM modelling strategies. These are informed by the internally calculated parametric fits	Model includes PartSA and StateTM modelling strategies. These are informed by models fit outside of Excel with estimates pasted in
PSA—time taken for 1000 PSA runs using base-case settings	1.42 min	13.2 min
One-way sensitivity analysis—time taken to run 109 parameter scenarios	0.27 min	2.4 min
Automatic report generation	Report template is set up within R Markdown to automatically populate tables and figures with active modelling analyses when selected	Highly challenging to include; not included
Quality control	Table included with selected diagnostic checks Linear code with vectors and data frames produced by single calculations that need to be checked once. However, tracing an individual calculation from start to finish can take longer than in Excel	Diagnostic checks included in the patient flow sheet Cell-by-cell checks were required across all sheets because of individual calculations, meaning there was potential for drag down error and inconsistency within columns and data frames

	Packages used are open-source: version to be used needs to be defined to ensure stability over time	
Model size	5.1 MB—includes R scripts and Excel input workbooks containing simulated PLD, general population survival statistics and cost inputs	30.9 MB—single workbook
Version control	Managed by the version control software Git to allow tracked changes, code reversions and parallel work streams	Manual change log. Multiple versions required to allow reversions. Difficult to work in parallel

Adapted from Hart et al. R and Shiny for Cost-Effectiveness Analyses: Why and When? A Hypothetical Case Stud[144]y

Abbreviations**:** MB megabytes, MCM mixture-cure modelling, PartSA partitioned survival analysis, PLD patient-level data, PSA probabilistic sensitivity analysis, StateTM state transition model

The EAG, however, note that R is less familiar than Excel to many stakeholders within the NICE process. To mitigate the potential impacts of lack of familiarity on model transparency the model input sheet has been designed in Excel and intermediate outputs (patient flow) will be provided in Excel.

The model is intended to be made open-access using 'GitHub' to improve replicability and collaboration. The model will be built broadly aligning with good practice guidelines, for example, the Zorginstituut Nederland National Health Care Institute (ZIN) guidelines for building models in R.[145]

Underlying data (model inputs) will not need to be publicly available and can be shared confidentially with NICE abiding to the principles for handling confidential information outlined in the 2022 manual.[32]The publicly available version of the decision model will use dummy data in the correct format as inputs where data are marked as either academic or commercial in confidence within the original data source. The dummy data will be created using the methods used to redact an Excel model as part of a NICE submission.

Data which are expected to need to be marked as confidential and redacted to reduce the potential for back-calculation of confidential prices include:

- PAS price discounts
- Any individual patient level data provided by the company

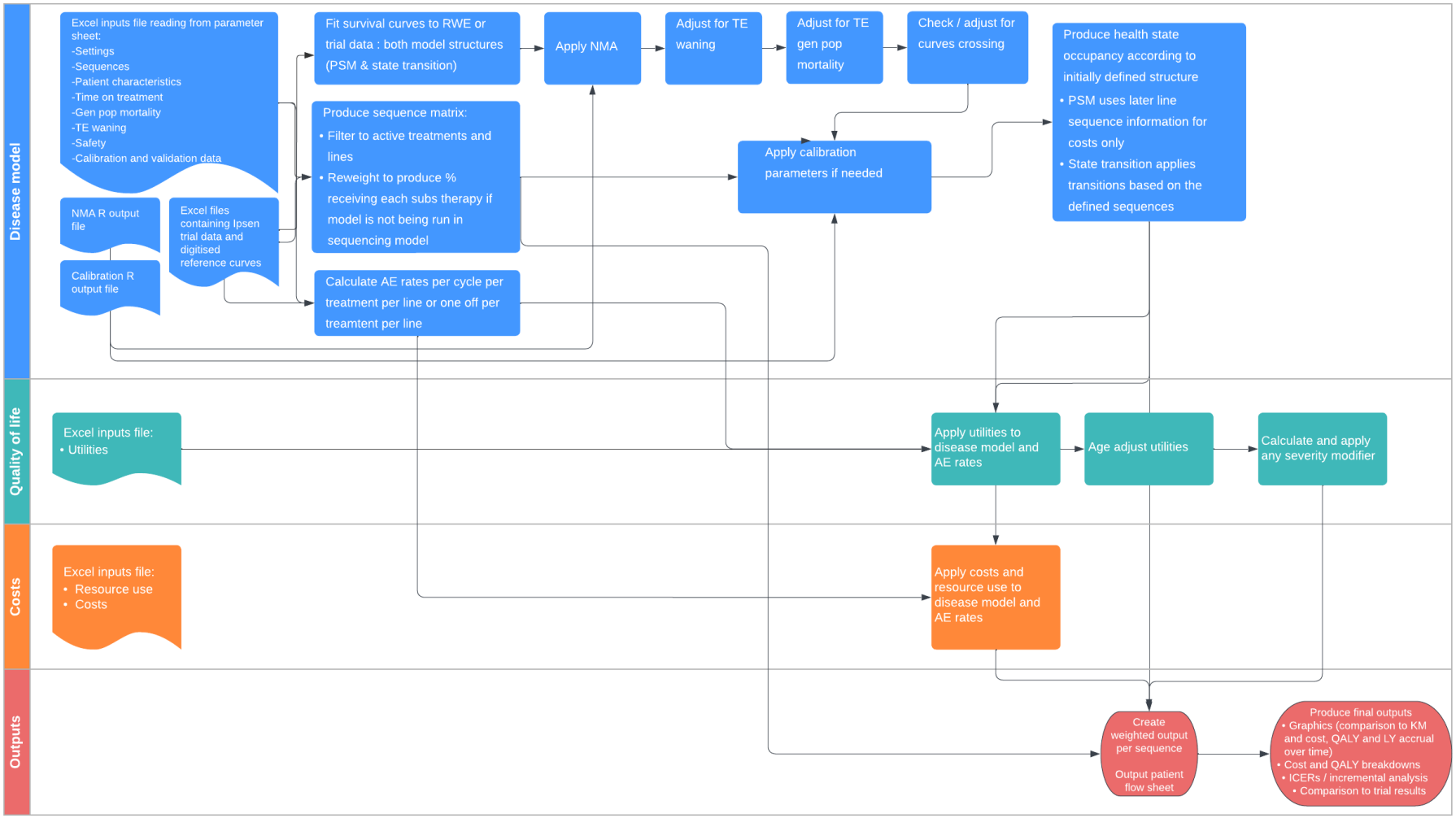
- Time on treatment input data
- Relative dose intensity input data
- Market share data for subsequent therapies
- Reported ICERs (PAS price and list price)

A later stage of this pilot following the evaluation of cabozantinib plus nivolumab will involve the incorporation of a Shiny front-end to the R model. This will allow model users to interact via an easy-to-understand user-interface operating via their web browser.

Figure 16 demonstrates the proposed model flow for each of the modules incorporated within the R model. Inputs to the decision model will come from four sources:

- The main Excel inputs workbook which will contain data and settings for the disease model, utilities and resource use and costs
- An Excel file containing pseudo patient level data for the reference curves for each population, treatment, trial, line and endpoint
- The R output file from the NMAs
- The R output file from any calibration exercises conducted

Figure 16: Model flow diagram



Abbreviations: AE, adverse event; NMA, network meta-analysis; RWE, real world evidence; TE, treatment effect

The methods for each of the models required to produce the desired outputs are described in detail in the sections below.

The cost effectiveness of the interventions will be estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per life year gained (LYG), net monetary benefit and net health benefit. Base case analyses will be probabilistic as this generates expected outcomes and costs and is in line with the NICE manual.[32]

Intermediate outputs including the patient flow sheet and graphical outputs such as fits to KM curves will be presented, as well as the final model outputs describing cost-effectiveness and its drivers.

5.3.2. Population

The model population will align with the decision problem population with results for the appraisal of cabozantinib plus nivolumab presented for relevant treatments for untreated advanced or metastatic RCC followed by a subsequent therapy mix reflective of actual or expected UK practice.

Subgroup analysis will be presented to align with the final scope as far as evidence allows for:

- intermediate-/poor-risk and favourable-risk subgroups as defined in the IMDC criteria
- prior treatment – this is not expected to be possible as data from CheckMate 9ER is not available for people receiving adjuvant pembrolizumab

Population characteristics are expected to be taken from a UK RWE data source rather than CheckMate 9ER in the model base case.

5.3.3. Treatments included

The treatments included within the decision model for the first-line setting align with those specified in the decision problem (Table 1 and Table 11).

Table 11: Treatments included within the decision model

Treatments	First-line population			Administration type and frequency	Treatment duration
	All risk	Fav risk	Poor / int risk		
Cabozantinib plus nivolumab[30]	x	x	x	Cabo: 40mg orally once daily Nivo: 240mg every 2 weeks or 480mg every 4 weeks IV	Until disease progression or unacceptable toxicity Max 24 months for nivo
Pazopanib[146]	x	x	x	800mg orally once daily	Until disease progression or unacceptable toxicity[26]
Tivozanib[147]	x	x	x	1340 mcg orally once daily for 21 days, followed by a 7-day rest period	Until loss of clinical benefit or unacceptable toxicity[18]
Sunitinib[148]	x	x	x	50mg orally once daily, for 4 consecutive weeks, followed by a 2-week rest period	Until disease progression or unacceptable toxicity[149]
Cabozantinib[30]			x	60mg orally once daily	Until disease progression or unacceptable toxicity
Nivolumab plus ipilimumab[150]			x	Nivo: 3 mg/kg IV every 3 weeks for the first 4 doses Ipi: 1 mg/kg IV every 3 weeks for the first 4 doses Nivo maintenance: 240mg every 2 weeks or 480mg every 4 weeks IV starting 3 or 6 weeks after the last dose of combination treatment respectively	Maximum 4 cycles of combination treatment Monotherapy until loss of clinical benefit or unacceptable toxicity[18]
Pembrolizumab plus lenvatinib[151,152]			x	Pembro: 200mg every 3 weeks of 400mg every 6 weeks IV Lenva: 20mg orally once daily	Until disease progression or unacceptable toxicity Max 35 3 weekly cycles for pembro[18] or equivalent number of 6-weekly cycles

Abbreviations: Cabo, cabozantinib; IV, intravenous; ipi, ipilimumab; lenva, lenvatinib; nivo, nivolumab; pembro, pembrolizumab

For subsequent lines of treatment (which may be comprised of either active drug treatment or BSC) the EAG will consider the following sources of data to determine what will be included within the decision model:

- UK RWE – preferred source
- Trial data from CheckMate 9ER
- Clinical expert input to determine which sequences of treatment are valid for use in practice

Subsequent surgeries and radiotherapy will not be considered as a line of treatment and will be included only as a cost according to the proportion of patients experienced to receive such treatment at each line.

5.3.4. Perspective, time horizon, cycle length, discounting and price year

The model will an NHS and Personal Social Services perspective in line with the NICE reference case. [32]

The time horizon for the economic analysis will be long enough to reflect any differences in costs or outcomes between the technologies under comparison. This is expected to be 40 years in line with the other recent appraisals for untreated advanced RCC TA858, TA780, TA650 and TA645.

A weekly cycle length will be applied to account for the difference in dosing regimens across treatments. This is consistent with TA858, TA780, TA650 and TA645. Half cycle correction will not be applied given the short cycle length.

Costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with the NICE manual. [32] All costs were expressed in UK pounds sterling for the 2022 price year (as the latest NHSCII inflation index was available only until 2022 during the time this report was prepared).

5.3.5. Treatment effectiveness and extrapolation

As shown in Figure 17 modelling of treatment effectiveness will require extrapolation of 4 different curves for the reference treatment at each line in the model base case:

- PFS (or TTNT as a proxy for PFS) – here both progression (or receipt of subsequent therapy) and death are classed as events
- TTP – here progression is classed as an event and death is classed as a censor variable
- TTD – here treatment discontinuation and death are classed as events
- Post progression survival (or post last line survival) for the last line of treatment – here the time measured starts from progression on the prior line and death is classed as an event

Within the scenario analysis using PartSA OS, PFS and TTD will require extrapolation for the reference curve at the first line of treatment only.

The reference treatment extrapolated for the first line is expected to be sunitinib given this is the comparator in the majority of the available RCTs and a treatment used in UK practice for all risk groups. The reference treatment for later lines has yet to be determined.

In line with the NICE manual[32] and discussion from other recent appraisals[153] data for the reference treatment will be taken from UK RWE if possible:

> *"Quantifying the baseline risk of health outcomes and how the condition would naturally progress with the comparator(s) can be a useful step when estimating absolute health outcomes in the economic analysis. This can be informed by observational studies. Relative treatment effects seen in randomised trials may then be applied to data on the baseline risk of health outcomes for the populations or subgroups of interest." NICE manual 2022*

> *"Specifically, the committee thought that using randomised data to estimate absolute event rates runs the risk of results that do not reflect NHS practice. It also thought that using observational data to estimate relative effects runs the risk of biased treatment effects because of unadjusted confounding variables. The committee noted that NICE's technical support document 13 makes this distinction, advocating registry data to estimate absolute baseline event rates and randomised evidence to quantify relative differences. The committee concluded that it still preferred using the real-world evidence to estimate survival for people having cabazitaxel and the network meta- analysis to estimate the relative treatment effect of cabazitaxel compared with lutetium-177" ID3840 ACD2*

5.3.5.1. Extrapolation of survival curves

Extrapolation of survival curves will be conducted in accordance with NICE TSD 14 and NICE TSD 21 with the latter taking precedent if it is determined that more flexible modelling methods are required. In order to determine if more flexible models are required the log-cumulative hazard plots will be examined – if they are not approximately straight lines then alternative approaches will be considered.

If standard parametric models are considered appropriate the following curves will be fitted in line with TSD 14: exponential, Weibull, lognormal, log-logistic, Gompertz, generalised gamma using the flexsurvreg package in R.

The base case survival curve for each endpoint at each line and in each population will be selected according to the following criteria which are listed in indicative priority order.

- Clinical validity – both in the biological plausibility of the trends in the hazard function considered via qualitative clinical input and in the absolute survival predicted versus quantitative clinical input from structured expert elicitation
- Consistency with longer term external data
- Consistency and validity across endpoints
    - Extrapolations where curves cross will be ruled out where possible
    - When using the PartSA approach the implications of selected OS and PFS curves on post progression survival and plausibility of this will be carefully considered
    - The overall modelled OS does not exceed the expected OS for the general population
- Statistical goodness of fit within trial (AIC and BIC)
- Visual inspection
- Statistical validity versus the NMA type to be applied (only the Weibull, exponential, generalised gamma and Gompertz curves are consistent with the application for a FP NMA)

More flexible survival models will be considered if these are deemed to be necessary. We will follow the guidance within TSD21: *"careful thought should be given to the biological and clinical justification to any statistical approach selected; the approaches detailed herein should not be*

considered as an extended list of survival methods to "try out" on data. Instead, care should be taken to think through the underlying mechanisms likely to be dictating short and long-term hazard survival functions."

The use of more flexible methods may be necessary for PFS in the first portion of the KM curve due to issues with initial steep drops caused by scanning protocols. The use of interval censoring would be the preferred option to deal with these issues, however, pursuing such a method is not feasible within the time scales of this project.

5.3.5.2. Time to treatment discontinuation

Time on treatment will be calculated in the base case using extrapolation of TTD curves where possible. A scenario analysis will be included using PFS curves given the low level of reporting of TTD information across trials.

Stopping rules apply for a number of treatments for RCC. Where this is the case, data on the number of doses taken will be used in preference to TTD data where available; where this has not been reported stopping rules will be applied after production of the expected TTD curve to calculate costs.

For combination therapies, in line with standard trial reporting, the TTD curve will only class patients as coming off treatment when both parts of the combination have been discontinued. We will account for the reduction in drug cost with early discontinuation of one part of the combination using RDI data for each drug within the combination.

Treatment breaks are often used to allow toxicities to settle. NHSE restricts the length of treatment breaks before therapy is restarted, people who have longer breaks are not able to restart therapy via the normal funding route. Breaks of up to 3 months are allowed for nivolumab plus ipilimumab and nivolumab monotherapy, 12 weeks for pembrolizumab plus lenvatinib and avelumab plus axitinib and 6 weeks for cabozantinib, tivozanib and lenvatinib plus everolimus. [18] Similar restrictions are expected for other TKIs not included in the CDF drugs list. Treatment breaks will be considered within the model using RDI data to account for the impact on cost. The impact on effectiveness is assumed to already be included within the TTD data used to populate the model as people on a break will still be classed as remaining on treatment.

In practice, people are able to discontinue 1st line TKI monotherapy and switch to another TKI. This is only possible when they have had immediate prior treatment with a TKI which has had to

be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression. [18] This is not expected to occur frequently and therefore these types of switches have been excluded from consideration within the decision model.

5.3.5.3. Calculation of relative treatment effectiveness

Treatment effectiveness for all other therapies will be calculated by applying the results of the NMA in the form of CODA samples. We will also explore the impact of assuming equal effectiveness between certain treatments in line with prior appraisals including:

- Pazopanib and sunitinib have similar effectiveness (TA858, TA645)
- Tivozanib is at best similar to pazopanib and sunitinib (TA858, TA645)
- Everolimus and axitinib have similar effectiveness (TA432, TA417)

5.3.5.4. Treatment effectiveness waning

Following application of NMA results we will consider the plausibility of the long-term treatment effect predicted for each of the treatments relative to the reference treatment. We will present the long-term treatment effect over time in the form of a plot of the time-dependent hazard ratio function.

The application of treatment effect waning assumptions will be considered for each treatment based upon:

- How long the treatment is given for
- The mechanism of action of the treatment and biological plausibility informed by clinical expert advice
- Consistency between treatments with similar mechanisms of action
- Precedent in prior appraisals

Precedent will be used to guide considerations. Table 12 demonstrates that within RCC, as in many other oncology indications, Committee concerns regarding uncertainty in long-term treatment effects in earlier submissions led to modelling of scenarios around TE waning in later submissions and assumptions becoming part of the base case where stopping rules for treatments were in place, follow-up was particularly short or OS curves crossed. We would note,

however, that even in TA858 where follow-up was longer and stopping rules did not apply the Committee considered exclusion of TE waning from the EAG base case to be uncertain.

Table 12: Precedent from prior appraisals on TE waning

TA	Treatment type	Stopping rule prior to progression?	OS follow-up	Committee considerations on TE waning
TA858	IO+TKI	No	Median 33 months	Excluded from EAG base case, Committee considered uncertain
TA780	IO+IO	Ipilimumab only given during first 4 cycles	Min 60 months	Death hazards between arms would be likely to equalise, probably between 4.5 and 21 years
TA650	IO+TKI	Yes	Median 13 months	5 year TE waning (also looked at 3 and 10 years) regardless of response
TA645	IO+TKI	No	Min 13 months	Excluded after removal of stopping rule, Committee request presented TE over time
TA542	TKI	No	Median 29 months OS curves crossed	Modelling should assume that there is no treatment effect beyond the observed survival data, which covered a duration of less than 4 years. EAG base case 5 year TE waning accepted
TA498	TKI+mTOR	No	> Median 25 months*	Lifetime treatment effect in EAG base case. Committee would have liked to have seen more conservative assumptions explored
TA463	TKI	No	Median 21 months	Assuming the effect of cabozantinib continues for up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival, was highly uncertain
TA417	IO	No	Median 17 – 18 months	Committee remained concerned that the company assumed a continual post-treatment benefit of nivolumab and had not presented to the Committee analyses that excluded this benefit

*Follow-up only reported for Dec 2014 data-cut, July 2015 data-cut used in model

Abbreviations: EAG, external assessment group; IO, immunotherapy; OS, overall survival; mTOR, mammalian target of rapamycin inhibitor; TE, treatment effect; TKI, tyrosine kinase inhibitor

Careful consideration will therefore be given to the duration of the treatment effect with the option included within the model to explore the potential impact of treatment effect waning (via either imposition of equal hazards between treatments at a set time point or a linear change in hazards towards the reference treatment between two timepoints').

5.3.5.5. Accounting for general population mortality

In addition to the base check that the predicted survivor function for OS does not exceed that of the general population we will ensure that the hazard function for OS does not fall below that of the general population for any of the modelled cycles.

As the EAG will not have access to cause-specific death data survival curves we will use a simple method (selection of the maximum hazard function for any time period) to account for any issue of patients with RCC being projected to live longer than those in the general population with the same age and sex mix at baseline. Other alternatives such as the relative survival models described in TSD21 require cause specific mortality data.

ONS life tables[154] will be used to calculate mortality for the general population with age and sex data for patients at the start of treatment taken from UK RWE if possible. We will model mortality separately by sex accounting for the differences in life expectancy by gender.

5.3.5.6. Adjustment for curves crossing

Whilst every effort will be made to ensure that curves do not cross during survival curve selection this may be unavoidable for outcomes where curves may close together (e.g. TTP, PFS and TTD). If this is the case, we will adjust curves such that TTD <= PFS and TTP <= PFS to remove any logical inconsistency.

5.3.5.7. Validation and calibration

We will present the final modelled curves vs Kaplan Meier data and compare outcomes for the restricted mean survival time, including for OS, based upon the aggregation of outcomes for each line of treatment to determine whether the model fit is appropriate.

The model curve will then be compared to the projections from other models previously used for NICE STAs in the same decision point. Dependent on what data are available from the review of RWD sources these data may either be used as a direct model input or within the validation exercise.

Given the proposed primary model structure (state transition), calibration to expected OS estimates may be required. If this is the case, we would propose to conduct this within a likelihood-based framework.

5.3.6. Adverse events

The impact of toxicity on both costs and quality of life will be included within the economic analysis. The impact of toxicity on discontinuation will be addressed through the TTD endpoint and not separately of other types of discontinuation given the data available.

Adverse events rates are expected to be taken from data supplied by Ipsen for CheckMate 9ER. In line with the data request these should account for cases where there are multiple events rather than just being the number of people experiences a specific type of adverse event. We would propose to include G3+ AEs which occur in more than 5% of patients in any trial arm in the model. This aligns with TA858. [19]

The data available for adverse events from UK RWE is expected to be limited, although one publication has been identified focussing on safety outcomes for IOs. [52]

Data are being extracted from other trials for broader measures of adverse events (AEs leading to treatment discontinuation and G3+ AEs) for NMA. This will provide a broad measure of relative toxicity.

Reporting of specific adverse events is inconsistent across the literature and producing NMAs per specific AE, given the number of interest, is not feasible therefore the following options are being considered to present the impact of toxicity within the model:

- Naïvely use AEs rates treatments outside of CheckMate 9ER based upon available published data – this is standard practice in the majority of oncology TAs
- Apply relative risks from the NMA vs CheckMate 9ER for G3+ AEs to the naïve AE rates extracted per type of AE for each treatment – preferred option

AEs may either be applied as a per cycle event rate or as a one-off cost and utility impact at the start of each treatment. We expect to explore both options and use clinical advice and published information on how AE rates vary over time to determine which is most appropriate.

These approaches are considered to give a reasonable approximation given that adverse events were not found to be a key model driver in any of the published literature.

The final costs and quality of life impacts for each treatment will be checked with clinical experts to ensure they hold face validity, if the experts indicate issues then scenarios provided by the experts will be considered.

5.3.7. Utility values

5.3.7.1. Literature search and data extraction

A total of 82 studies were identified in the literature containing utility values for people with advanced RCC (1st, 2nd and subsequent lines of therapy). To identify relevant and generalisable utility values for inclusion within the model, a set of prioritisation criteria was established. Based on this criteria, UK and NICE technology appraisals, European and Western (non-European) studies containing utility values (published from 2017 onwards) were considered most relevant for consideration. Using the prioritisation criteria, 34 studies were identified.

- UK studies from 2017 including NICE TAs (n=12)
- Europe (non-UK) studies from 2017 (n=8)
- Western studies from 2017 (non-European) (n=14)

Two UK studies by Meng et al. (2018) [155] and Amdahl et al. (2017) [156] were excluded from consideration for inclusion in the decision model. The study by Meng et al., which estimated the cost effectiveness of cabozantinib compared to axitinib, everolimus and nivolumab, in adults with advanced RCC who have experienced failure on prior therapy, reported utilities for 2nd line patients that lacked face validity when compared to other data sources (considered too high). The average utility for patients without disease progression was 0.817 and post progression utility was estimated to be 0.777. Furthermore, HRQoL data were elicited directly from participants in the METEOR trial using the EQ-5D-5L, however these values were not mapped to EQ-5D-3L, as per NICE methods guidance. [32] The study by Amdahl et al., which estimated the cost effectiveness of pazopanib compared to sunitinib for the treatment of metastatic renal cell carcinoma (1st line) was also excluded. Utilities were not elicited directly from patients in the COMPARZ trial, but were estimated using incidence and adverse event data from COMPARZ and a regression equation based on EQ-5D assessments from a pivotal trial which compared pazopanib to placebo. The study did not report a utility value for progression free, however the value for progressed disease was reported to be 0.5509, which was considered unreasonably

low when compared with progressed disease utilities in other published literature sources and NICE TAs.

From the European (non UK) studies, one study by Porta et al, [157] presented HRQoL data from the CheckMate 9ER study. The study was a matched adjusted indirect comparison of HRQoL of cabozantinib plus nivolumab compared to pembrolizumab plus axitinib which is not a treatment of interest to this analysis. HRQoL was elicited directly from patients using the EQ-5D and FKSI-DRS. This study was excluded from consideration for use within the decision model as no absolute values were reported. Furthermore, the visual analogue scale (VAS) was used as the valuation method which does not align with NICE preferred methods. All European (non UK) studies were excluded due to limitations including values not being reported in a manner suitable for model input, use of secondary data sources for utility estimates, no direct elicitation from patients and lack of EQ-5D-5L mapping. For similar reasons, Western (non Europe) studies were not considered for use in the analysis. For the complete list of prioritisation studies including rationale for inclusion/exclusion, see the utilities data extraction grid in Appendix D.

Based on the literature search, ten published NICE TA's were identified that met the prioritisation criteria (Table 13). There was some variability in progression free and progressed utilities across NICE TAs for 1st line treatments (and amongst 2nd line treatments), this appeared to be due to heterogeneity across clinical trials with respect to patient characteristics including risk score. Utilities within these appraisals were presented primarily according to health state/progression status, however in TA650 a time to death (TTD) approach was used. Treatment specific utility values were not commonly used within NICE aRCC appraisals, though this approach was adopted in TA780. In order to be congruent with aRCC TAs submitted to NICE, our model estimates utility based on health state/progression status. Furthermore, NICE TAs were considered as the primary source for utility data, until company data from CheckMate 9ER has been received (see Section 4.3.7.2 for more detail).

Table 13: Utility values in published NICE TAs

TA	Year	Recommendation Population	Intervention	Source of utilities	Utilities
TA858	2023	1L	Lenvatinib plus pembrolizumab	CLEAR trial (EQ-5D-3L)	Redacted
TA830	2022	Adjuvant: increased risk of recurrence after nephrectomy	Pembrolizumab	KEYNOTE 564 (EQ-5D-5L mapped to EQ-5D-3L)	Disease free: 0.868 PFS (distant metastases): 0.803 PD (distant metastases): 0.772
TA780 (CDF review of TA581)	2022	1L int/poor risk	Nivolumab plus ipilimumab	Checkmate 214 (EQ-5D-3L)	PFS on/off nivolumab and ipilimumab: 0.793 on and 0.749 off PFS on/off sunitinib: 0.754 on and 0.707 off PPS off nivolumab and ipilimumab: 0.702 PPS off sunitinib: 0.707
TA650	2020	1L	Pembrolizumab plus axitinib	Manufacturer derived utility values from KEYNOTE 426 (EQ-5D-3L). A time to death approach was used in the company's base case.	Redacted NICE noted that use of utilities from KEYNOTE 426 and published literature were acceptable for decision making.
TA645	2020	1L	Avelumab plus axitinib	JAVELIN Renal 101 (EQ-5D-5L mapped to EQ-5D-3L)	PFS: 0.753 PD: 0.683
TA542	2018	1L int/poor risk	Cabozantinib	TIVO-1(EQ-5D-3L)	PFS: 0.726 PD: 0.649
TA512	2018	1L	Tivozanib	TIVO-1 (EQ-5D-3L)	PFS: 0.726 PD: 0.649
TA498	2018	2L (1 prior VEGF, ECOG 0-1)	Lenvatinib plus everolimus	AXIS (EQ-5D, version unclear)	PFS: 0.69 PD: 0.61
TA463	2017	2L/3L (Prior VEGF)	Cabozantinib	METEOR (EQ-5D-5L)	PFS: 0.817 PD: 0.777
TA432	2017	2L	Everolimus	Swinburn et al (2010) [158]	SD: 0.795 PD: 0.36

Abbreviations: PFS, progression free survival; PD, progressed disease; SD, stable disease

5.3.7.2. Utilities used in the model

Prior to receipt of company data from CheckMate 9ER, the most appropriate sources identified for the base case analyses are TA645 for patients treated at first line and TA498 for patients treated at second line. We opted to derive utilities from these NICE TAs on the basis that the utilities for first and second line demonstrated face validity, were elicited directly from patients using the EQ-5D and were assessed and accepted by NICE. In TA645, quality of life data were collected directly from patients in the JAVELIN Renal 101 study using the EQ-5D-5L. Values were then appropriately mapped to the EQ-5D-3L using the Van Hout crosswalk algorithm, [159] resulting in a PFS utility of 0.753 and a PD value of 0.683. These utilities are in broad alignment with the utilities used in TA512 for tivozanib and TA542 for cabozantinib. We noted that in TA498, utilities were not collected in the pivotal trial HOPE 205 and that the values used within that appraisal were taken from the AXIS trial (for axitinib). Although this may be considered a limitation (as HRQoL was not elicited directly from patients in HOPE 205), the EAG and NICE concluded that utilities from AXIS were appropriate for use in the analysis. We noted that PFS utility in TA498 for 2nd line treatment (0.69) was higher than the PD utility reported in TA645 for 1st line treatment (0.683), thus presenting a logical inconsistency. To mitigate this, our analysis therefore assumes that progression free patients at 2nd line will have a utility of 0.683, reflective of progressed 1st line patients.

To estimate the PD utility in second line and subsequent lines, we used the approach outlined in NICE DSU12 guidance, [160] which states that when utility values from cohorts with combined health states are not available*, 'the multiplicative method should be used to combine the data from subgroups with the single health conditions (p.22)'*. In our analysis, the % reduction in utility (from moving from PFS to PD) in TA498 was used applied i.e. 2nd line utility was estimated as follows 0.69/0.683*0.61=0.616. Due to a lack of robust, published utility values for people receiving third line treatment (or later), the same approach was used to estimate PD utility in later lines.

For third line, the PFS utility value was assumed to be reflective of the progressed disease value for second line patients, that is 0.616. As described previously, to estimate the progressed disease value, we applied the percentage reduction in moving from PFS to progressed in TA498, to the PFS utility value, which resulted in a third line progressed disease utility value of 0.545 (see Table 13).

For fourth line, the PFS utility value was assumed to be reflective of the progressed disease value for 3rd line patients, that is 0.545. To estimate the progressed disease value we applied the percentage reduction in moving from PFS to progressed disease in TA498, to the PFS utility value, which resulted in a fourth line progressed disease utility value of 0.482 (see Table 13). This value is consistent with palliative care utility estimates within oncology submissions to NICE.

The decision to apply the percentage reduction in utility (in moving from PFS to progressed disease) from TA498 to estimate utility values for progressed disease at second, third line and fourth line, was to ensure logical consistency, that is, to ensure patient utility decreases with disease progression.

Due to a lack of published HRQoL data for carers and to be consistent with previous NICE appraisals for advanced RCC, our analysis did not include carer disutility.

Utility values were adjusted for age and sex using the published equation by Ara and Brazier et al (2010) [161] and the Health Survey England (HSE) 2014 dataset, as per Hernandez Alava et al (2022). [162] Disutility due to adverse events will be considered in the analysis once these data have been provided by the company.

Table 14: Utility values proposed to be used in the model

Line of treatment	Utility	Source
First line	PFS: 0.753 PD: 0.683	JAVELIN Renal 101(TA645[94])
Second line	PFS: 0.683 PD: 0.616	PFS utility assumed to reflect PD in 1st line. PD value estimated based on % reduction from the AXIS trial (TA498[97])
Third line	PFS: 0.616 PD: 0.545	Estimated based on % reduction from the AXIS trial (TA498).Approach follows NICE DSU12 guidance[160])
Fourth line	PFS: 0.545 PD:0.482	Estimated based on % reduction from the AXIS trial (TA498).Approach follows NICE DSU12 guidance[160])

PFS, Progression free survival; PD, Progressed disease

5.3.8. Resource use and costs

5.3.8.1. Results from literature search and data extraction

A total of 13 studies were identified in the literature containing cost and resource use data (Section 5.1.1.3, Figure 13) for people with advanced RCC across different lines of therapy (namely first, second and subsequent lines), of which there were ten NICE TAs and three published studies. Subsequent data extraction from these studies was performed. All of the identified studies were found to be UK based and adopted an NHS and PSS perspective. The costs included comprised of drug and administration costs, disease management or health state costs based on the healthcare resource utilised and terminal care costs. Some studies also reported adverse event costs and subsequent therapy costs. Resource use frequency was sourced from one of the following sources: clinical trial or its post-hoc analysis, previous NICE technology appraisals or feedback from clinical experts. Unit costs associated with the healthcare resource use were derived from NHS reference costs and Unit costs of Health and Social Care from PSSRU etc. Summary of cost and resource use information from published studies has been provided in Table 15 and from previous NICE technology appraisals has been provided in Table 16. Detailed data extraction tables are provided in Appendix D.

It can be noted that the source of unit costs, medicine costs and terminal costs were consistent across the published studies as well as the previous NICE technology appraisals. However, the source of resource use frequency was quite varied across the studies. Table 17 in Section 5.3.8.2, therefore compares the different sources for resource use inputs and provides rationale for selecting specific inputs.

Further, in the following sections, the selection of appropriate sources and specific inputs for each type of costs used in the model has also been discussed briefly.

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Table 15: Summary of cost and resource use information from published studies

	Amdahl 2017	**Edwards 2018 [NICE TA463]**	**Meng 2018**
Setting/country	UK	UK	England, UK
Intervention	Pazopanib	For patients who have received previous cytokine therapy (aldesleukin or interferon alfa): axitinib, sorafenib, sunitinib, BSC For people who have received previous VEGF-targeted therapy: axitinib, cabozantinib, everolimus, nivolumab, sunitinib	Cabozantinib
Comparator	Sunitinib	The interventions listed above compared with each other and BSC	Axitinib Everolimus Nivolumab
Patient population	Treatment-naïve patients with mRCC consistent with that of the COMPARZ trial	Patients with previously treated amRCC who received previous VEGFR-targeted therapy	Adult patients with aRCC following prior VEGFR-targeted therapy
Cohort/Sample size	1,100 (COMPARZ)	Sample size of the included studies ranged from 14 to 362	1,096
Perspective	NHS and PSS	NHS and PSS	NHS and PSS
Price year	2014	2015	2017 (not explicitly stated but assumed, as prices were inflated to 2017)
Currency	GBP	GBP	GBP
Discount rate	3.5%	3.5%	3.5%
Type of costs included	• Costs of treatment initiation, medication, and dispensing for pazopanib and sunitinib • Pre-progression follow-up and monitoring, other mRCC-related care associated with pazopanib and sunitinib treatment during PFS, post-progression supportive	• Drug and administration costs • Disease management costs • Terminal care costs • Adverse events costs and • Subsequent therapy costs	• Drug and administration costs • Disease management/health state costs • Terminal care costs and • Adverse events costs

	care, and in a sensitivity analysis, post-treatment anti-cancer therapy		
Source of resource use estimates	MRU data sourced from post-hoc analysis of COMPARZ trial. [163] Data collected included medical office visits, laboratory visits and tests, home healthcare, hospitalization, urgent care, and medical/surgical procedures.	Previous NICE TAs complemented by expert clinical opinion sought by AG	Source of resource use frequency not reported
Source of unit costs	National Schedule of Reference Costs for 2011–2012, [164] adjusted to 2014 prices using the Consumer Price Index (CPI) for health. [165]	NHS reference costs 2014-15, [166] PSSRU 2015[167]	NHS reference costs 2014-15, [166] PSSRU 2015[167]
Source of medicine costs	List prices of pazopanib and sunitinib from BNF. For pazopanib, the list price was adjusted to reflect 12.5% PAS discount[26] and for sunitinib the first treatment cycle (i.e., 28 days of treatment in first 6 weeks) was provided at no cost. [149]	BNF	BNF Dosing and administration schedules from relevant trials, publications, or NICE TAs[54,90,168]
Source of terminal care costs	Terminal care costs not considered	Based on Nuffield Trust report 2014[169]	Based on Nuffield Trust report 2014

Abbreviations: UK, United Kingdom; BSC, Best supportive care; amRCC, advanced metastatic Renal Cell Carcinoma; VEGFR, Vascular Endothelial Growth Factor Receptor; NHS, National Health Services; PSS, Personal Social Services; GBP, British Pounds; MRU, Medical Resource Use; TA, Technology appraisal; AG, Assessment Group; PSSRU, Personal Social Services Research Unit; BNF, British National Formulary; PAS, Patient Access Scheme.

Table 16: Summary of cost and resource use information from previous NICE technology appraisals

NICE TA #	Year	Patient population	Type of costs included	Source of resource use estimates	Source of unit costs	Source of medicine costs	Source of terminal care costs
TA858	2023	1L int/poor risk, where nivolumab plus ipilimumab would otherwise be offered	Drug costs, Admin and health state costs, AE costs, End of life costs	TA650	PSSRU 2020, NHS reference costs 2019-20	BNF	Based on Nuffield Trust report 2014 inflated to 2019/20 costs
TA830	2022	Adjuvant: increased risk of recurrence after nephrectomy	Drug acquisition costs, administration costs, disease management costs, costs for managing adverse events, subsequent treatment costs and terminal care costs incurred at the end of life	KEYNOTE 564, TA650, clinical expert opinion	PSSRU 2020, NHS reference costs 2019-20	BNF, Dosing from SmPC	Based on Nuffield Trust report 2014 inflated to 2019/20 costs
TA780	2022	1L int/poor risk	Drug costs, Admin and health state costs, AE costs, End of life costs	TA581	Not reported	BNF	Not reported
TA650	2020	1L (not recommended)	Drug acquisition and administration of first line and subsequent treatments, with adjustment for dose intensity; monitoring and disease management in PF and PD states; treatment of included TEAEs for first-line treatments; and terminal care costs in the last cycle before death	TA542 and clinical expert opinion	PSSRU 2018 and NHS reference costs 2017-18	BNF, dosing from SmPC	Based on Nuffield Trust report 2014 inflated to 2019/20 costs
TA645	2020	1L	Drug costs, Admin and health state costs, AE costs, End of life costs	Aligned with TA581	PSSRU 2018, NHS reference costs 2017-18	BNF	Addicott et al. 2008
TA581	2019	1L int/poor risk	Drug and admin costs, health state costs, subsequent treatment costs and AE costs	TA333 and TA417	PSSRU 2015 and 2017, NHS reference costs 2015-16 and 2016-17	BNF	Based on Nuffield Trust report 2014, inflated to 2016/2017

TA542	2018	1L int/poor risk	Drug and treatment costs, health state unit costs and resource use, AE costs and resource use, Subsequent treatment costs and Terminal care costs	Estimated by UK clinicians, aligned with TA512 and TA215	PSSRU 2016, NHS reference costs 2016-17	BNF	Based on Nuffield Trust report 2014, inflated to 2017
TA512	2018	1L	Drug and treatment costs, health state unit costs and resource use, AE costs and resource use, Subsequent treatment costs	TA333	PSSRU 2015, NHS reference costs 2015-16	BNF	Not reported
TA498	2018	1 prior VEGF, ECOG 0-1	Drug and treatment costs, health state unit costs and resource use, AE costs and resource use, Subsequent treatment costs and Terminal care costs	TA333	PSSRU 2015, NHS reference costs 2015-16	BNF	Based on Nuffield Trust report 2014, inflated to 2016
TA463	2017	Prior VEGF	Drug and treatment costs, health state unit costs and resource use, AE costs and resource use, Subsequent treatment costs and Terminal care costs	Estimated by UK clinicians	PSSRU 2015, NHS reference costs 2015-16	BNF	Based on Nuffield Trust report 2014, inflated to 2016
TA432	2017	Prior VEGF	Drug and treatment costs, health state unit costs and resource use, AE costs and Terminal care costs	SLR and economic evaluation, 2008[170]	PSSRU 2015, NHS reference costs 2014-15	BNF	Guest et al. and Coyle et al.

Abbreviations: AE, Adverse events; PSSRU, Personal Social Services Research Unit, BNF, British National Formulary; NHS, National Health Services; SmPC, Summary of Product Characteristics; TA, Technology appraisal.

5.3.8.2. Disease management or health state costs

The quantum of health state resource use (i.e., medical oncologist outpatient consultations, CT scans, blood tests etc.) was found to differ across the included studies. A comparison especially of the consultant outpatient follow-up and CT scans pre- and post-progression between the estimates from previous NICE TAs[19,96,98] which had detailed description of the health care resource use with the individual components broken down and the BMJ and ESMO published RCC guidelines, [22,23] has been presented below in Table 17. As can be seen, a noticeable variation was observed in the resource use frequency within the NICE TAs and when compared to the published guidelines as well. For instance, while the ESMO RCC guideline recommended a consultant follow up visit every 2-4 months, BMJ RCC guideline indicated that it could be best judged by the treating clinician and in the previous NICE TAs the observed frequency of follow up visit ranged from every month to every three months.

Table 17: Comparison of long term follow up frequency across key published studies/NICE TAs and RCC guidelines

Heath state	Resource type	Resource use frequency				
		NICE TA463[98]	**NICE TA542[96] & TA858[19]**	**Edwards 2018[171]**	**BMJ RCC guideline[22]**	**ESMO RCC guideline[23]**
Pre-progression (on and off treatment	Consultant outpatient follow up	0.67 per 4-week cycle (~every 6 weeks)	0.25 per week (~every month)	Every 3 months	Left to judgement of treating clinician	Every 2 to 4 months
	CT scan	0.33 per 4-week cycle (~every 3 months)	0.08 per week (~every 3 months)	Every 3 months	Few monthly intervals	Every 2 to 4 months
Post-progression (off treatment)	Consultant outpatient follow up	Not included*	0.25 per week (~every month)	Not included	Left to judgement of treating clinician	Every 2 to 4 months
	CT scan	Not included*	0.08 per week (~every 3 months)	Not included	Few monthly intervals	Every 2 to 4 months
	GP and specialist nurse visit	1 per 4-week cycle (every month)	Not applicable	20 visits per year (only specialist nurse visit)	Not discussed	Not discussed

Abbreviations: NICE, National Institute of Health and Care Excellence; TA, Technology appraisal; RCC, Renal Cell Carcinoma, BMJ, British Medical Journal; ESMO, European Society for Medical Oncology

*TA463 was conducted in previously-treated patients at a time where few options were available, therefore post-progression here essentially represents BSC and patients were assumed to be discharged from the oncology.

Note: There was no clear reason reported for why there is a difference in resource use frequency between NICE TA463 and Edwards 2018 (the related EAG monograph), however, it looks likely that the clinical expert opinion to EAG matured over time as Edwards 2018 indicated that estimates based on TA333 and TA417 were complemented by clinical expert opinion to AG (however such a statement was not explicitly available in NICE TA463)

The health state costs and resource use estimates used in the model (Table 18) were based on NICE TA542[96], TA858[19] and Edwards 2018, [171] which will also be complemented by the clinical expert opinion to be sought by EAG at a later stage.

When initiating a new line of treatment patients would have an initial visit with the medical oncologist (including a blood test), then a subsequent visit where tolerability to the new treatment would also be assessed (in line with standard practice of a formal medical review to determine tolerability[18]), followed by subsequent monthly follow up visits (while acknowledging some patients might need to be seen more or less frequently). It is to be noted that given the advanced stage of the disease, a 4-weekly follow up frequency was deemed appropriate which is also consistent with NICE TA858. [19] Patients would also receive CT scans every 3 months (which was found to be almost consistent across the included studies) to check for the signs of progression and a routine blood test every 4 weeks aligned with the consultant visits.

The frequency of consultant follow-up visits, CT scans and blood tests was assumed to be the same across all lines of treatment, as monitoring would broadly remain the same irrespective of the treatment received (consistent with NICE TA 858). In addition, patients were assumed to have daily pain medication and regular specialist nurse visits in line with Edwards 2018, however, only during the last line of treatment prior to death. These assumptions will be checked with clinical experts.

Table 18: Health states resource use and unit costs

Health state	Resource type	Frequency of use (per week)	Unit cost (2021 costs inflated to 2022)	Source
First week of treatment, all lines	Consultant outpatient visit (first visit)	1	£379.78	Frequency: NICE TA858 Unit cost: NHS reference costs 2020-21; HRG code WF01B, Nephrology - Non-Admitted Face-to-Face Attendance, First
	Blood test	1	£2.16	Frequency: NICE TA 858 Unit cost: NHS reference costs 2020-21; HRG code DAPS 03 - Integrated blood services
All lines of treatment, on and off treatment	Consultant outpatient follow up	0.25	£150.31	Frequency: NICE TA542, NICE TA858 Unit cost: NHS reference costs 2020-21; HRG code WF01A, Nephrology - Non-Admitted Face-to-Face Attendance, Follow up
	CT scan	0.083	£171.54	Frequency: NICE TA542, NICE TA858 Unit cost: NHS reference costs 2020-21; HRG code RD27Z – CT scan of more than three areas
	Blood test	0.25	£2.16	Frequency: NICE TA542, NICE TA858 Unit cost: NHS reference costs 2020-21; DAPS 03 - Integrated blood services
Last line of treatment	Specialist nurse visit	0.5	£53	Frequency: Based on Edwards 2018 but assumed to be twice as frequent as consultant follow up Unit cost: PSSRU 2022, [172] Section 11.2.2 Nurse specialist (Band 6), cost per working hour
	Pain medication	7 (1 mg/ml vial of morphine sulphate per day)	£5.78	Frequency: Based on Edwards 2018 Unit cost: BNF; 50 mg/50 ml vial of morphine sulphate solution for infusion

Abbreviations: NICE, National Institute of Health and Care Excellence; TA, Technology appraisal; BNF, British National Formulary; NHS, National Health Services; PSSRU, Personal Social Services Research Unit

Note: 2020-21 costs were inflated to 2022 using NHSCII annual % increase on previous year index (2.72%) from PSSRU 2022 [172]

5.3.8.3. End of life costs

End of life or terminal care costs are incurred by all patients dying in the model based on the Nuffield Trust report exploring the cost of care at the end of life. [169] All the previous published studies and the NICE TAs (except TA645) derived terminal care cost from this report (as seen in Table 16).

The cost components of terminal care per the Nuffield Trust report have been given below in Table 19. All costs are presented from an NHS / PSS perspective and were inflated to 2022 costs using the NHS cost inflation indices (NHSCII) from PSSRU. [172] The total estimated cost of terminal care (inflated to 2022) was found to be £8,714.

Table 19: Summary of costs related to end-of life or terminal care

Resource type	Resource use frequency*, Mean (SD)	Unit cost per patient	Source	Total costs (adjusted for inflation)
GP consultation	11.4 (6.2) visits	£42	Resource use frequency: Nuffield Trust report, 2014. [169] [Table 1, Group: Cancer diagnosis] Unit cost: PSSRU 2022, [173] Section 9.4 GP unit costs – patient contact lasting 9.22 minutes, including direct care staff and with qualification costs	£479
District nursing care	7.53 (19.57) hours	£53	Resource use frequency: Nuffield Trust report, 2014. [Table 2, Group: Cancer diagnosis] Unit cost: PSSRU 2022, [173] Section 11.2.2 Nurse specialist (Band 6), cost per working hour	£399
Local authority funded social care	Not available	£444 (£1,484)	Cost: Nuffield Trust report, 2014. [Table 3, Group: Cancer diagnosis; 2010 costs]	£549
Hospital care	Not available	£5,890 (£5,264)	Cost: Nuffield Trust report, 2014. [Table 4, Group: Cancer diagnosis; 2010 costs]	£7,287
Total				**£8,714**

Abbreviations: GP, General Practitioner; PSSRU, Personal Social Services Research Unit

* number of visits or cost of care in the last 90 days before death

Note: 2010 costs were inflated to 2022 by applying year on year annual % increase on the 2014/15 HCHS index = 293.1 from PSSRU 2017[174] (which resulted in 2022 index = 332.3)

5.3.8.4. Drug and administration costs

A summary of acquisition costs of the treatments considered in the first line setting and their respective dosing schedules (as provided in detail in Table 11, Section 5.3.3), along with the

treatments in subsequent lines has been presented in Table 20 below. Please note that the unit costs for each drug were extracted from either the drugs and pharmaceutical electronic market information tool (eMIT) or the British National Formulary (BNF) and the cheapest unit price was used where multiple formulations existed for the same drug. Except for everolimus and sunitinib (for which the costs were derived from eMIT), all other drug costs were sourced from BNF.

The per cycle costs for each drug component were calculated based on the respective dosing regimen/intensities and were applied to proportion of patients remaining on treatment in each model cycle within the modelled time horizon (informed by the TTD curve). The dosing regimens are the same across the favourable and intermediate/poor risk subgroups, RDIs are expected to be assumed equivalent across subgroups (this assumption will be checked once company data are received).

The model will include confidential PAS and commercial access arrangement discounts (where applicable) as received from NICE with the ICER containing all discounted prices presented in a confidential appendix.

Table 20: Acquisition costs of treatments considered in the model

Treatment	Formulation	Size of pack	Dose per unit	Pack price[175,176]
Avelumab	Bavencio® 200 mg/10 ml infusion vials	1 vial	20 mg per ml	£768
Axitinib	Inlyta® 5 mg tablets	56 tablets	5 mg	£3,517
Cabozantinib	Cabometyx® 40 mg	30 tablets	40 mg	£5,143
Everolimus	Everolimus 10 mg tablets (Sandoz Ltd)	30 tablets	10 mg	£373.48
Ipilimumab	Yervoy® 50mg/10 ml infusion vials	1 vial	5 mg per ml	£3,750
Lenvatinib	Lenvima® 10 mg capsules	30 capsules	10 mg	£1,437
Nivolumab	Opdivo® 100mg/10 ml infusion vials	1 vial	10mg per ml	£1,097
	Opdivo® 40mg/4 ml infusion vials	1 vial	10 mg per ml	£439
Pazopanib	Votrient® 400 mg tablets	30 tablets	400 mg	£1,121

Treatment	Formulation	Size of pack	Dose per unit	Pack price[175,176]
Pembrolizumab	Keytruda® 100mg/4 ml infusion vials	1 vial	25 mg per ml	£2,630
Sunitinib	Sunitinib 50 mg capsules (Zentiva pharma UK Ltd)	28 capsules	50 mg	£1,388.77
Tivozanib	Fotivda® 1340 µg capsules	21 capsules	1.34 mg	£2,052

Abbreviations: NHS, National Health Service; mg, milligrams; ml, millilitres; UK, United Kingdom.

Relative dose intensities will be applied to calculate the actual cost of the treatments consistent with the previous NICE technology appraisals and clinical trial data, as provided in Table 21.

Table 21: Relative dose intensities of treatments considered

Drug	Relative dose intensity, % (SE where available)	Source
Avelumab + axitinib	Avelumab: 91.5 Axitinib: 89.4	Motzer et al 2019[65]
Axitinib	99	AXIS trial: Rini et al. 2011[54]
Cabozantinib	93.3 (9.3)	NICE TA542
Everolimus	84 (1.1)	METEOR trial: Choueiri et al 2015[66]
Lenvatinib + everolimus	Lenvatinib: 70.4 Everolimus: 89.3	CLEAR trial: Motzer et al 2021[60]
Lenvatinib + pembrolizumab	Lenvatinib: 69.6 Pembrolizumab: 62.9 – median number of infusions reported as 22	CLEAR trial: Motzer et al 2021[60]
Nivolumab	97.5 (9.8)	NICE TA417
Nivolumab + cabozantinib	Awaiting company data	
Nivolumab + ipilimumab	Nivolumab induction: 79*; Nivolumab maintenance: Same as nivo in nivo + cabo (assumption) Ipilimumab: 79*	Motzer et al 2018[59] For nivo, same RDI as nivo+cabo to be assumed for nivo mono maintenance as data not available
Pazopanib	86 (8.6)	NICE TA215
Sunitinib	87 (6.3)	NICE TA542
Tivozanib	94	NICE TA512

Abbreviations: SE, standard error

*79% reported to receive all 4 doses of nivolumab and ipilimumab within the induction phase

It is to be noted that different administration modes were used for different drugs depending on its route of administration and whether or not the drug is administered jointly based on NICE TA858, which has been provided below in Table 22, along with the unit costs extracted from NHS reference costs 2020-21. Administration costs will be applied to the proportion of patients

remaining on treatment in each model cycle that drug is received within the modelled time horizon.

Table 22: Unit cost of drug administration

Treatments	Administration mode	Unit cost (2021 cost inflated to 2022)	Source
Pembrolizumab, nivolumab, avelumab	Simple parenteral Chemotherapy at First Attendance - Outpatient	£288.76	NHS reference costs 2020-21; HRG code: SB12Z
Ipilimumab (for first 4 cycles when nivolumab is delivered jointly with ipilimumab)	Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£541.33	NHS reference costs 2020-21; HRG code: SB14Z
Lenvatinib, sunitinib, pazopanib, tivozanib, axitinib and cabozantinib	Exclusively Oral Chemotherapy + Pharmacist (Band 6) assuming 12 minutes	£262.26	NHS reference costs 2020-21; HRG code: SB11Z. Pharmacist time based on NICE TA645

Abbreviations: HRG, Healthcare resource group; IV, intravenous; NHS, National Health Service.

Note: 2020-21 costs were inflated to 2022 using NHSCII annual % increase on previous year index (2.72%) from PSSRU 2022[172]

5.3.8.5. Adverse event costs

AE management costs will be calculated using the unit costs per event and the rate of AEs for each treatment under consideration (for the two options explained in Section 5.3.6). The model will include options to explore AE costs being applied per cycle (based on the per cycle event rates) or as a one-off cost.

Table 23 presents the costs of adverse events as per NICE TA858, with the costing assumptions informed by NICE TA551 and the unit costs derived from NHS reference costs 2020-21. The EAG considered TA858 to be a reasonable starting point as it provided a comprehensive list of adverse events to be considered while awaiting the CheckMate 9ER trial data and adverse event data extraction from the SLR completed for this appraisal. The below list will be revised once these data are available.

Table 23: Adverse event costs per event

AE	Cost per event (2021 costs inflated to 2022)	Assumptions (costing assumptions based on NICE TA551) [177]
Anaemia	£808.02	Weighted average SA04G-L. Iron Deficiency Anaemia, Non-elective stay + nurse (GP practice) cost per hour
Asthenia	£1010.38	Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay + nurse (GP practice) cost per hour
Decreased appetite	£1058.38	Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay + dietician cost per session
Diarrhoea	£714.93	Weighted average FD10A-M Non-Malignant Gastrointestinal Tract Disorders without Interventions, non-elective short-stay
Dyspnoea	£1010.38	Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay + nurse (GP practice) cost per hour
Fatigue	£1010.38	Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay + nurse (GP practice) cost per hour
Hyperglycemia	£737.14	Weighted average SA08G-J. Other Haematological or Splenic Disorders. Non-elective short stay + nurse (GP practice) cost per hour
Hypertension	£786.94	EB04Z. Hypertension. Non-elective short stay + 1* WF01A, Nephrology - Non-Admitted Face-to-Face Attendance, outpatient, Follow up + 2* General practitioner – cost per surgery consultation lasting 9.22 minutes – including direct care staff costs, with qualification costs
Hypertriglyceridaemia	£737.14	Weighted average SA08G-J. Other Haematological or Splenic Disorders. Non-elective short stay + nurse (GP practice) cost per hour
Increased ALT	£1023.43	Weighted average of GC17G-K. Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions. Non-elective short stay+ 1* WF01A, Nephrology - Non-Admitted Face-to-Face Attendance, outpatient, Follow up- + Average of computerised tomography currency codes (adult only; one area only) weighted by activity (RD20A, RD21A, RD22Z)
Increased amylase	£810.07	Weighted average of GC17G-K. Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions. Non-elective short stay + nurse (GP practice) cost per hour
Increased AST	£810.07	Weighted average of GC17G-K. Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions. Non-elective short stay + nurse (GP practice) cost per hour
Increased lipase	£810.07	Weighted average of GC17G-K. Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions. Non-elective short stay + nurse (GP practice) cost per hour
Lymphocytopenia	£833.70	Weighted average of SA35A-E Agranulocytosis. Non-elective short stay + nurse (GP practice) cost per hour

AE	Cost per event (2021 costs inflated to 2022)	Assumptions (costing assumptions based on NICE TA551) [177]
Nausea	£877.23	FD10K Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 6-10. Non-elective short stay.
Neutropenia	£833.70	Weighted average of SA35A-E Agranulocytosis. Non-elective short stay + nurse (GP practice) cost per hour
Palmar-plantar syndrome	£599.88	JD07J Skin Disorders without Interventions, with CC score 2-5. Non-elective short stay.
Platelet count decrease	£905.99	Weighted average SA12G-K. Thrombocytopenia. Non-elective short stay.
Proteinuria	£861.13	Weighted average cost of LA09M-Q. General Renal Disorders without Interventions. Non-elective short stay + 1* WF01A, Nephrology - Non-Admitted Face-to-Face Attendance, outpatient, Follow up
Stomatitis	£958.38	Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay
Weight decreased	£698.50	Weighted average FD04A-E. Non-elective short stay.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Note: 2020-21 costs were inflated to 2022 using NHSCII annual % increase on previous year index (2.72%) from PSSRU 2022[172]

5.3.8.6. Subsequent treatment costs

This section cannot be completed prior to receipt of company and observational data. It is planned for UK RWE to be used for subsequent therapies in the model base case to better reflect practice.

5.3.9. Severity

The NICE manual is unclear as to how current practice should be defined in a multi-comparator decision space such as is present here for calculation of the severity modifier. There are three clear options to define current practice in these circumstances given that QALY data must be taken from the economic model and not external literature:

- Define a common reference treatment to calculate severity modifiers for all other treatments compared to this
- Calculate the severity modifier based upon the market shares of all the comparators
- Calculate severity modifiers separately for pairwise comparisons

Use of pairwise comparisons, whilst being the simplest option, is inconsistent with the principle of fully incremental analysis. Use of market shares would also be inconsistent with the principle of fully incremental analysis. Therefore, we propose that absolute and proportional shortfall will be calculated using a common reference treatment for the overall population and each risk subgroup with QALY weightings assigned based upon NICE's severity modifiers (Table 24). The reference treatment to which cabozantinib plus nivolumab is compared will be the treatment with the largest absolute QALYs which is not ruled out via the rules of dominance / extended dominance within incremental analysis. This represents current best practice.

Table 24: QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Abbreviations: QALY, quality-adjusted life-year

The future health lost by people living with RCC will be calculated using age and sex data taken from UK RWE if possible. ONS life tables (2018 – 2020) [154] will be used to calculate future life expectancy for the general population and the HSE 2014 dataset will be used to calculate future

quality of life for the general population. [162] QALYs for the general population will be discounted at a rate of 3.5%, consistent with modelled QALYs for RCC treatments.

Modelled discounted QALYs for the reference treatment will then be used to calculate absolute and proportional QALY shortfall amounts and the relevant QALY modifier to apply.

5.3.10. Uncertainty

Base case analyses will be probabilistic as this generates expected outcomes and costs and is in line with the NICE manual. [32] Additional scenario and one-way sensitivity analyses will be conducted where they add value and clarity.

6. COST-EFFECTIVENESS RESULTS

6.1. Model validation and face validity check

Initially, model outputs will be compared to the data used as model inputs (for example visual comparison to Kaplan Meier data) to ensure the appropriateness of model structure and data derivation. The model will then be compared to the projections from other models previously used for NICE STAs in the same decision point. Dependent on what data are available from the review of RWD sources these data may either be used as a direct model input or within the validation exercise.

Clinical expert input will be used to ensure that the model retains clinical face validity.

If stakeholders have any data they consider to be useful for validation, we would request this to be supplied in response to this report.

6.2. Benefits not captured in the QALY calculation

No benefits have been identified at this stage that can be included within the QALY calculation, however, we have noted concerns from early clinical consultation that the impact of toxicities may be fully reflected in previous economic analyses.

7. DISCUSSION AND CONCLUSIONS

The major considerations identified so far for this appraisal include:

- Modelling methods, and outcomes of the cost-effectiveness analyses of various combinations, vary across the available literature including within prior NICE TAs. This underlines the benefit of a common modelling framework as far as practicable to enable consistency of decision making using the best available data at the time
- Comparators for cabozantinib plus nivolumab differ by risk status (combination therapies are only available outside of the CDF for intermediate / poor risk), which necessitates comparison by risk status; data for favourable risk patients appears, however, to be less well reported
- Earlier treatment options affect what is available at later lines and may also impact on outcomes at later lines; data to be able to model the latter impact appears to be limited and prior appraisals have failed to meet Committee preferences to use UK data for the type of subsequent therapy received and to match costs and effectiveness
- The outcomes demonstrated with RCTs showed greater absolute benefit than those demonstrated in SACT in a previous appraisal indicating that use of RCT data for baseline risk may lead to an overestimate of benefit for treatments – sourcing of UK RWE to model baseline risk is therefore a project priority
- The assumption of proportional hazards may not hold within RCC meaning that more complex methods for NMA will be explored
- There were issues with implausible extrapolations across prior TAs meaning that input from clinical experts, external data and face validity tests needs to be prioritised when conducting survival curve analysis, including careful attention to application of treatment effect waning
- Relatedly, the duration of treatment effect for newer combination treatments is uncertain, assumptions used within prior appraisals have varied; it may be that the optimal approach varies by line

- Our general modelling approach represents a shift from partitioned survival models to state transition models, though we intend to preserve functionality for partitioned survival models. This 'return' to state transition models creates is necessary in order to have the flexibility to meet NICE's objective to create a model capable of looking at the entire treatment pathway, though it also adds additional challenges in obtaining appropriate data and ensuring the plausibility of predictions of OS

This report is based only upon publicly available data and is very much a work in progress. The EAG are expecting additional data to be supplied by Ipsen relating to this appraisal and to access a number of UK RWE sources. Any data that are received in time for incorporation within this appraisal will be considered, assessed for relevance and quality and included to supplement each of the sections presented within this report.

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Appendix A: Literature search strategies

Clinical effectiveness searches: systematic reviews and meta-analyses

Ovid MEDLINE(R) ALL <1946 to December 19, 2022>

Search date: 19 December 2022

#	Search terms	hits
1	exp renal cell carcinoma/	38967
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79433
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50496
4	or/1-3	85754
5	exp Kidney Neoplasms/co, dt, pc, th [Complications, Drug Therapy, Prevention & Control, Therapy]	24002
6	exp antineoplastic agents/	1224683
7	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	2918163
8	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	4058024
9	exp nivolumab/	4780
10	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	9104
11	exp Ipilimumab/	2762
12	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	5188
13	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	8075
14	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	1797
15	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	847
16	exp axitinib/	689
17	(axitinib or Inlyta or "AG-013736").mp.	1402
18	(cabozantinib or cometriq or cabometyx or XL184).mp.	1459

19	exp sunitinib/	4073
20	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	7243
21	(pazopanib or Votrient or "GW786034B").mp.	2218
22	(tivozanib or Fotivda or AV951 or "AV?951").mp.	150
23	exp everolimus/	5540
24	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	8786
25	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	53
26	or/5-25	6153895
27	(systematic review or meta-analysis).pt.	294997
28	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	332150
29	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	296051
30	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	14743
31	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	36779
32	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	37881
33	(handsearch* or hand search*).ti,ab,kf.	10835
34	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	33973
35	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	11663
36	(meta regression* or metaregression*).ti,ab,kf.	13549
37	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	438050
38	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	319211
39	(cochrane or (health adj2 technology assessment) or evidence report).jw.	21080
40	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	16821
41	(outcomes research or relative effectiveness).ti,ab,kf.	10926

42	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	4168
43	(meta-analysis or systematic review).mp.	410085
44	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	285
45	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	177
46	umbrella review*.ti,ab,kf.	1226
47	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	13
48	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	18
49	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	11
50	or/27-49	644080
51	("Case Reports" or Comment or Editorial or "Historical article" or Letter).pt. or "case report".ti.	4587898
52	4 and 26 and 50	1486
53	52 not 51	1394
54	limit 53 to yr="2018 -Current"	628

Database: Embase <1974 to 2022 December 19>

Search date: 19 December 2022

#	Search terms	hits
1	exp renal cell carcinoma/	31174
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114211
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77252
4	or/1-3	128712
5	exp kidney cancer/dm, dt, si, th [Disease Management, Drug Therapy, Side Effect, Therapy]	28575
6	exp antineoplastic agent/	2638818
7	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	3623259
8	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	6000219
9	exp nivolumab/ (32745)	32745
10	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	34448

11	exp Ipilimumab/	21936
12	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	22838
13	exp pembrolizumab/	31244
14	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	32860
15	exp lenvatinib/	5387
16	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	5629
17	exp avelumab/	5280
18	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	5482
19	exp axitinib/ (6639)	6639
20	(axitinib or Inlyta or "AG-013736").mp.	6844
21	exp cabozantinib/	6024
22	(cabozantinib or cometriq or cabometyx or XL184).mp.	6307
23	exp sunitinib/	26404
24	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	27267
25	exp pazopanib/	10059
26	(pazopanib or Votrient or "GW786034B").mp.	10323
27	exp tivozanib/	782
28	(tivozanib or Fotivda or AV951 or "AV?951").mp.	814
29	exp everolimus/	31492
30	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	35736
31	exp belzutifan/	144
32	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	173
33	or/5-32	8690322
34	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	576741
35	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	362049
36	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	17188
37	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	51879
38	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	46313
39	(handsearch* or hand search*).ti,ab,kf.	13182
40	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	44792
41	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	18756

42	(meta regression* or metaregression*).ti,ab,kf.	16660
43	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	687084
44	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	415676
45	(cochrane or (health adj2 technology assessment) or evidence report).jw.	29538
46	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	24545
47	(outcomes research or relative effectiveness).ti,ab,kf.	15635
48	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	7108
49	(meta-analysis or systematic review).mp.	649107
50	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	410
51	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	256
52	umbrella review*.ti,ab,kf.	1294
53	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	27
54	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	19
55	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	22
56	or/34-55	926571
57	("Case Reports" or Comment or Editorial or "Historical article" or Letter).pt. or "case report".ti.	2348064
58	4 and 33 and 56	3089
59	58 not 57	2999
60	limit 59 to yr="2018 -Current"	1550
61	"Conference Abstract".pt.	4623992
62	60 not 61	1153

The Cochrane Library
Search date: 20 December 2022

#1 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees 1064
#2 ((renal or kidney) NEAR/3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)):ti,ab 4049
#3 ("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma"):ti,ab 3634
#4 #1 or #2 or #3 4674
#5 MeSH descriptor: [Antineoplastic Agents] explode all trees13346
#6 (efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic):ti,ab 1171199
#7 MeSH descriptor: [Nivolumab] explode all trees 615
#8 (nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538") 2650
#9 MeSH descriptor: [Ipilimumab] explode all trees 278

#10 (ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010") 1692
#11 (pembrolizumab or keytruda or "MK-3475" or "SCH 900475") 2623
#12 (lenvatinib or kisplyx or E7080 or "E?7080") 535
#13 (avelumab or bavencio or MSB0010718 or "MSB?0010718C") 351
#14 MeSH descriptor: [Axitinib] explode all trees 112
#15 (axitinib or Inlyta or "AG-013736") 391
#16 (cabozantinib or cometriq or cabometyx or XL184) 475
#17 MeSH descriptor: [Sunitinib] explode all trees 353
#18 (sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248") 1379
#19 (pazopanib or Votrient or "GW786034B") 626
#20 (tivozanib or Fotivda or AV951 or "AV?951") 85
#21 MeSH descriptor: [Everolimus] explode all trees 1645
#22 (everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD) 4442
#23 (Belzutifan or Welireg or MK-6482 or PT2977) 26
#24 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 1173781
#25 #4 and #24 3904
[CDSR only – 21]

INAHTA
Search date: 20 December 2022

(((Belzutifan or Welireg or MK-6482 or PT2977)) OR ((everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD)) OR ("Everolimus"[mhe]) OR ((tivozanib or Fotivda or AV951)) OR ((pazopanib or Votrient or "GW786034B")) OR ((sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248")) OR ("Sunitinib"[mhe]) OR ((cabozantinib or cometriq or cabometyx or XL184)) OR ((axitinib or Inlyta or "AG-013736")) OR ("Axitinib"[mhe]) OR ((avelumab or bavencio or MSB0010718)) OR ((lenvatinib or kisplyx or E7080)) OR ((pembrolizumab or keytruda or "MK-3475" or "SCH 900475")) OR ((ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010")) OR ("Ipilimumab"[mhe]) OR ((nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538")) OR ("Nivolumab"[mhe]) OR ((efficacy or effectiveness or treatment or therapy or management or chemotherapy or adjuvant or antineoplastic)) OR ("Antineoplastic Agents"[mhe])) AND (("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear cell" or "non clear cell" or hypermephroma or "hypernephroid carcinoma")) OR ("Carcinoma, Renal Cell"[mhe]) OR (renal AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma)) OR ((kidney AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma))))

NICE website
Search date: 20 December 2022
"Renal cell cancer" or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma"
= 19 hits

Clinical effectiveness searches: RCT update

Database(s): Ovid MEDLINE(R) ALL 1946 to January 24, 2023
Search date: 24 January 2023

1	exp renal cell carcinoma/	39158
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	80072
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50958
4	or/1-3	86420
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	1641447
6	4 and 5	31916
7	exp Kidney Neoplasms/co, dt, pc, th [Complications, Drug Therapy, Prevention & Control, Therapy]	24060
8	exp antineoplastic agents/	1227896
9	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	2938616
10	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	4096120
11	exp nivolumab/	4852
12	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	9273
13	exp Ipilimumab/	2785
14	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	5252
15	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	8260
16	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	1862
17	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	866
18	exp axitinib/	693
19	(axitinib or Inlyta or "AG-013736").mp.	1419
20	(cabozantinib or cometriq or cabometyx or XL184).mp.	1492
21	exp sunitinib/	4080
22	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	7304
23	(pazopanib or Votrient or "GW786034B").mp.	2242
24	(tivozanib or Fotivda or AV951 or "AV?951").mp.	151
25	exp everolimus/	5557

26	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	8834
27	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	59
28	or/7-27	6200040
29	randomized controlled trial.pt.	585212
30	controlled clinical trial.pt.	95167
31	randomized.ab.	591414
32	placebo.ab.	235411
33	clinical trials as topic.sh.	200787
34	randomly.ab.	401088
35	trial.ti.	278624
36	or/29-35	1501489
37	exp animals/ not humans.sh.	5086917
38	36 not 37	1381740
39	6 and 28 and 38	2481
40	limit 39 to yr="2021 -Current"	242

Database(s): **Embase** 1974 to 2023 January 24
Search date: 24 January 2023

1	exp renal cell carcinoma/	32303
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	115687
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	78350
4	or/1-3	130164
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	2275045
6	4 and 5	52032
7	exp kidney cancer/dm, dt, si, th [Disease Management, Drug Therapy, Side Effect, Therapy]	28397
8	exp antineoplastic agent/	2668623
9	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	3673455
10	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	6093092

11	exp nivolumab/	33065
12	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	34741
13	exp Ipilimumab/	22024
14	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	22903
15	exp pembrolizumab/	31561
16	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	33154
17	exp lenvatinib/	5505
18	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	5743
19	exp avelumab/	5274
20	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	5478
21	exp axitinib/	6638
22	(axitinib or Inlyta or "AG-013736").mp.	6833
23	exp cabozantinib/	6097
24	(cabozantinib or cometriq or cabometyx or XL184).mp.	6376
25	exp sunitinib/	26429
26	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	27293
27	exp pazopanib/	10073
28	(pazopanib or Votrient or "GW786034B").mp.	10326
29	exp tivozanib/	785
30	(tivozanib or Fotivda or AV951 or "AV?951").mp.	816
31	exp everolimus/	34534
32	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	35731
33	exp belzutifan/	145
34	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	174
35	or/7-34	8811247
36	randomized controlled trial/	758418
37	controlled clinical trial/	467789
38	36 or 37	949778
39	random$.ti,ab.	1898448
40	randomization/	97591
41	intermethod comparison/	289405

42	placebo.ti,ab.	356715
43	(compare or compared or comparison).ti.	588139
44	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2661384
45	(open adj label).ti,ab.	104744
46	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	267773
47	double blind procedure/	204605
48	parallel group$1.ti,ab.	31127
49	(crossover or cross over).ti,ab.	121233
50	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	401383
51	(assigned or allocated).ti,ab.	472848
52	(controlled adj7 (study or design or trial)).ti,ab.	434290
53	(volunteer or volunteers).ti,ab.	276455
54	human experiment/	625877
55	trial.ti.	386205
56	or/39-55	5942974
57	56 not 38	5150491
58	(random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	9226
59	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	327625
60	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	20848
61	(Systematic review not (trial or study)).ti.	239429
62	(nonrandom$ not random$).ti,ab.	18474
63	"Random field$".ti,ab.	2845
64	(random cluster adj3 sampl$).ti,ab.	1492

65	(review.ab. and review.pt.) not trial.ti.	1057775
66	"we searched".ab. and (review.ti. or review.pt.)	46507
67	"update review".ab.	134
68	(databases adj4 searched).ab.	57516
69	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1200754
70	Animal experiment/ not (human experiment/ or human/)	2521342
71	or/58-70	4179582
72	57 not 71	4467947
73	6 and 35 and 72	6279
74	limit 73 to yr="2021 -Current"	888

Cochrane Central
Search date: 25 January 2023
ID Search
#1 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees
#2 ((renal or kidney) NEAR/3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)):ti,ab
#3 ("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma"):ti,ab
#4 #1 or #2 or #3
#5 (advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four"):ti,ab
#6 #4 and #5
#7 MeSH descriptor: [Antineoplastic Agents] explode all trees
#8 (efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic):ti,ab
#9 MeSH descriptor: [Nivolumab] explode all trees
#10 (nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538")
#11 MeSH descriptor: [Ipilimumab] explode all trees
#12 (ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010")
#13 (pembrolizumab or keytruda or "MK-3475" or "SCH 900475")
#14 (lenvatinib or kisplyx or E7080 or "E?7080")
#15 (avelumab or bavencio or MSB0010718 or "MSB?0010718C")
#16 MeSH descriptor: [Axitinib] explode all trees
#17 (axitinib or Inlyta or "AG-013736")

#18 (cabozantinib or cometriq or cabometyx or XL184)
#19 MeSH descriptor: [Sunitinib] explode all trees
#20 (sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248")
#21 (pazopanib or Votrient or "GW786034B")
#22 (tivozanib or Fotivda or AV951 or "AV?951")
#23 MeSH descriptor: [Everolimus] explode all trees
#24 (everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD)
#25 (Belzutifan or Welireg or MK-6482 or PT2977)
#26 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
#27 #6 and #26 with Publication Year from 2021 to 2023, in Trials

Clinicaltrials.gov
Search date: 7 March 2023
Search terms: random OR rct OR randomly OR randomised OR randomized | Interventional Studies | Renal Cell Cancer Metastatic | pazopanib OR tivozanib OR sunitinib OR cabozantinib OR nivolumab OR ipilimumab OR lenvatinib OR pembrolizumab OR axitinib OR everolimus OR avelumab
= 125 hits

WHO ICTRP
Search date: 7 March 2023
Title: random OR randomized OR randomised OR randomisation OR randomization OR RCT
Condition: (renal cell OR kidney) AND (cancer OR carcinoma)
Intervention: pazopanib OR tivozanib OR sunitinib OR cabozantinib OR nivolumab OR ipilimumab OR lenvatinib OR pembrolizumab OR axitinib OR everolimus OR avelumab
= 442 records for 155 trials

Economic studies: economic evaluations

Database(s): Ovid MEDLINE(R) ALL 1946 to January 09, 2023
Search date: 9 January 2023

#	Searches	Results
1	exp renal cell carcinoma/	39067
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79756
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50731
4	or/1-3	86085
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	1634422
6	4 and 5	31811
7	exp Kidney Neoplasms/co, dt, pc, th [Complications, Drug Therapy, Prevention & Control, Therapy]	24032
8	exp antineoplastic agents/	1226142
9	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	2927184
10	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	4075456
11	exp nivolumab/	4822
12	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	9197
13	exp Ipilimumab/	2772
14	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	5215
15	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	8170
16	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	1829
17	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	861
18	exp axitinib/	691
19	(axitinib or Inlyta or "AG-013736").mp.	1414
20	(cabozantinib or cometriq or cabometyx or XL184).mp.	1474
21	exp sunitinib/	4077
22	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	7276
23	(pazopanib or Votrient or "GW786034B").mp.	2233
24	(tivozanib or Fotivda or AV951 or "AV?951").mp.	152
25	exp everolimus/	5549

26	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	8808
27	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	55
28	or/7-27	6174505
29	Economics/	27484
30	"costs and cost analysis"/	51061
31	Cost allocation/	2017
32	Cost-benefit analysis/	91428
33	Cost control/	21659
34	Cost savings/	12669
35	Cost of illness/	31192
36	Cost sharing/	2713
37	"deductibles and coinsurance"/	1846
38	Medical savings accounts/	547
39	Health care costs/	43742
40	Direct service costs/	1217
41	Drug costs/	17301
42	Employer health costs/	1097
43	Hospital costs/	11907
44	Health expenditures/	23560
45	Capital expenditures/	2001
46	Value of life/	5797
47	exp economics, hospital/	25665
48	exp economics, medical/	14376
49	Economics, nursing/	4013
50	Economics, pharmaceutical/	3092
51	exp "fees and charges"/	31278
52	exp budgets/	14065
53	(low adj cost).mp.	82135
54	(high adj cost).mp.	18878
55	(health?care adj cost$).mp.	15660
56	(fiscal or funding or financial or finance).tw.	188804
57	(cost adj estimate$).mp.	2676
58	(cost adj variable).mp.	50
59	(unit adj cost$).mp.	3031
60	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	389987
61	or/29-60	897051
62	(editorial or letter or case report or clinical conference or review).pt.	4916431
63	exp "systematic review"/ or exp meta analysis/	296555

64	(systematic or meta* or "mixed treatment comparison" or "indirect treatment comparison").ti,ab.	3349855
65	62 not (63 or 64)	4302209
66	(6 and 28 and 61) not 65	305
67	limit 66 to yr="2009 -Current"	271

Database(s): Embase 1974 to 2023 January 09, 2023
Search date: 9 January 2023

#	Searches	Results
1	exp renal cell carcinoma/	31521
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114590
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77537
4	or/1-3	129231
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	2252114
6	4 and 5	51612
7	exp kidney cancer/dm, dt, si, th [Disease Management, Drug Therapy, Side Effect, Therapy]	28662
8	exp antineoplastic agent/	2648585
9	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ti.	3635889
10	(efficacy or effectiveness or treatment* or therap* or management or chemotherap* or adjuvant or antineoplastic).ab. /freq=2	6026332
11	exp nivolumab/	33112
12	(nivolumab or "anti-PD-1 human monoclonal antibody MDX-1106" or "Opdivo" or "Opdivo Injection" or "NIVO" or "BMS-936558" or "MDX-1106" or "ONO-4538").mp.	34839
13	exp Ipilimumab/	22138
14	(ipilimumab or "anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody" or "MOAB CTLA-4" or "monoclonal antibody CTLA-4" or Yervoy or "MDX-CTLA-4" or "BMS-734016" or "MDX-010").mp.	23050
15	exp pembrolizumab/	31637
16	(pembrolizumab or keytruda or "MK-3475" or "SCH 900475").mp.	33277
17	exp lenvatinib/	5462
18	(lenvatinib or kisplyx or E7080 or "E?7080").mp.	5707
19	exp avelumab/	5358
20	(avelumab or bavencio or MSB0010718 or "MSB?0010718C").mp.	5564
21	exp axitinib/	6691

22	(axitinib or Inlyta or "AG-013736").mp.	6897
23	exp cabozantinib/	6091
24	(cabozantinib or cometriq or cabometyx or XL184).mp.	6378
25	exp sunitinib/	26506
26	(sunitinib or Sutent or "SU11248" or "SU011248" or "SU11248").mp.	27375
27	exp pazopanib/	10114
28	(pazopanib or Votrient or "GW786034B").mp.	10378
29	exp tivozanib/	788
30	(tivozanib or Fotivda or AV951 or "AV?951").mp.	820
31	exp everolimus/	31601
32	(everolimus or Zortress or Certican or Afinitor or Votubia or "RAD 001" or RAD001 or SDZ-RAD or SDZRAD or SDZ RAD).mp.	35873
33	exp belzutifan/	146
34	(Belzutifan or Welireg or MK-6482 or PT2977).mp.	175
35	or/7-34	8723841
36	Socioeconomics/	157038
37	Cost benefit analysis/	92471
38	Cost effectiveness analysis/	174213
39	Cost of illness/	20913
40	Cost control/	74692
41	Economic aspect/	121653
42	Financial management/	119686
43	Health care cost/	217619
44	Health care financing/	13782
45	Health economics/	35027
46	Hospital cost/	24546
47	(fiscal or financial or finance or funding).tw.	271614
48	Cost minimization analysis/	3871
49	(cost adj estimate$).mp.	4050
50	(cost adj variable$).mp.	309
51	(unit adj cost$).mp.	5343
52	or/36-51	1077979
53	(chapter or "conference review" or editorial or erratum or letter or note or "case report" or methodology or "clinical protocol" or nonhuman or "short survey" or "practice guideline" or review).pt,ti.	7322646
54	exp "systematic review"/ or exp meta analysis/	509695
55	(systematic or meta* or "mixed treatment comparison" or "indirect treatment comparison").ti,ab.	4111380
56	53 not (54 or 55)	6435399
57	"conference abstract".pt.	4650391

58	("american association for cancer research" or aacr or "american society of clinical oncology" or asco or "american urological association" or aua or esmo or "european association of urology" or eau or "genitourinary cancers symposium" or "international conference on translational cancer medicine" or "international society for pharmacoeconomics and outcomes research" or ispor).nc.	316614
59	57 not 58	4334100
60	6 and 35 and 52	1067
61	60 not (56 or 59)	931
62	limit 61 to yr="2009 -Current"	866

Economic studies: utilities

Database(s): Ovid MEDLINE(R) ALL 1946 to January 09, 2023
Search date: 9 January 2023

#	Searches	Results
1	exp renal cell carcinoma/	39067
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79756
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50731
4	or/1-3	86085
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	1634422
6	4 and 5	31811
7	"Value of Life"/	5797
8	Quality of Life/	257015
9	quality of life.ti,kf.	110630
10	((instrument or instruments) adj3 quality of life).ab.	3834
11	Quality-Adjusted Life Years/	15318
12	quality adjusted life.ti,ab,kf.	16684
13	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	26843
14	disability adjusted life.ti,ab,kf.	4934
15	daly*.ti,ab,kf.	4456
16	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	29912
17	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	2555

18	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	604
19	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	7393
20	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	39
21	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	448
22	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	22951
23	(hye or hyes).ti,ab,kf.	76
24	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	48
25	(pqol or qls).ti,ab,kf.	450
26	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	692
27	nottingham health profile*.ti,ab,kf.	1222
28	sickness impact profile.ti,ab,kf.	1091
29	exp health status indicators/	340260
30	(health adj3 (utilit* or status)).ti,ab,kf.	88742
31	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	15264
32	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	13811
33	disutilit*.ti,ab,kf.	593
34	rosser.ti,ab,kf.	107
35	willingness to pay.ti,ab,kf.	8121
36	standard gamble*.ti,ab,kf.	906
37	(time trade off or time tradeoff).ti,ab,kf.	1616
38	tto.ti,ab,kf.	1350
39	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1892
40	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	21519
41	duke health profile.ti,ab,kf.	92
42	functional status questionnaire.ti,ab,kf.	129
43	dartmouth coop functional health assessment*.ti,ab,kf.	13
44	or/7-43	730445
45	6 and 44	659
46	(editorial or letter or case report or clinical conference or review).pt.	4916431
47	exp "systematic review"/ or exp meta analysis/	296555
48	(systematic or meta* or "mixed treatment comparison" or "indirect treatment comparison").ti,ab.	3349855

49	46 not (47 or 48)	4302209
50	45 not 49	632
51	exp animals/ not humans.sh.	5080261
52	50 not 51	630
53	limit 52 to yr="2009 -Current"	497

Database(s): Embase 1974 to 2023 January 09
Search date: 9 January 2023

#	Searches	Results
1	exp renal cell carcinoma/	31521
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114590
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77537
4	or/1-3	129231
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	2252114
6	4 and 5	51612
7	socioeconomics/	157038
8	exp Quality of Life/	615092
9	quality of life.ti,kf.	172098
10	((instrument or instruments) adj3 quality of life).ab.	5284
11	Quality-Adjusted Life Year/	33347
12	quality adjusted life.ti,ab,kf.	25354
13	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	42369
14	disability adjusted life.ti,ab,kf.	5901
15	daly*.ti,ab,kf.	5727
16	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	48537
17	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	2848
18	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	993
19	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	11770

20	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	67
21	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	510
22	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	37025
23	(hye or hyes).ti,ab,kf.	165
24	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	55
25	(pqol or qls).ti,ab,kf.	730
26	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	859
27	nottingham health profile*.ti,ab,kf.	1645
28	nottingham health profile/	621
29	sickness impact profile.ti,ab,kf.	1279
30	sickness impact profile/	2372
31	health status indicator/	3400
32	(health adj3 (utilit* or status)).ti,ab,kf.	115941
33	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	24379
34	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	18145
35	disutilit*.ti,ab,kf.	1184
36	rosser.ti,ab,kf.	139
37	willingness to pay.ti,ab,kf.	12249
38	standard gamble*.ti,ab,kf.	1201
39	(time trade off or time tradeoff).ti,ab,kf.	2329
40	tto.ti,ab,kf.	2129
41	(hui or hui1 or hui2 or hui3).ti,ab,kf.	2960
42	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	35879
43	duke health profile.ti,ab,kf.	117
44	functional status questionnaire.ti,ab,kf.	169
45	dartmouth coop functional health assessment*.ti,ab,kf.	13
46	or/7-45	945003
47	6 and 46	1793
48	(chapter or "conference review" or editorial or erratum or letter or note or "case report" or methodology or "clinical protocol" or nonhuman or "short survey" or "practice guideline" or review).pt,ti.	7322646
49	exp "systematic review"/ or exp meta analysis/	509695
50	(systematic or meta* or "mixed treatment comparison" or "indirect treatment comparison").ti,ab.	4111380
51	48 not (49 or 50)	6435399

52	"conference abstract".pt.	4650391
53	("american association for cancer research" or aacr or "american society of clinical oncology" or asco or "american urological association" or aua or esmo or "european association of urology" or eau or "genitourinary cancers symposium" or "international conference on translational cancer medicine" or "international society for pharmacoeconomics and outcomes research" or ispor).nc.	316614
54	52 not 53	4334100
55	47 not (51 or 54)	1406
56	exp animal/ not human/	5197941
57	55 not 56	1400
58	limit 57 to yr="2009 -Current"	1173

Economic studies: UK costs

Database(s): Ovid MEDLINE(R) ALL 1946 to January 09, 2023
Search date: 9 January 2023

#	Searches	Results
1	exp renal cell carcinoma/	39067
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79756
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50731
4	or/1-3	86085
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	1634422
6	4 and 5	31811
7	(cost? adj2 (illness or disease or sickness)).tw.	4713
8	(burden? adj2 (illness or disease? or condition? or economic*)).tw.	52154
9	("quality-adjusted life years" or "quality adjusted life years" or QALY?).tw.	16193
10	Quality-adjusted life years/	15318
11	"cost of illness"/	31192
12	Health expenditures/	23560
13	(out-of-pocket adj2 (payment? or expenditure? or cost? or spending or expense?)).tw.	6449
14	(expenditure? adj3 (health or direct or indirect)).tw.	10563
15	((adjusted or quality-adjusted) adj2 year?).tw.	27647
16	or/7-15	137065

17	exp United Kingdom/	387636
18	(national health service* or nhs*).ti,ab,in.	259084
19	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	47472
20	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	2385721
21	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	1690052
22	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	67819
23	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	249038
24	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	32543
25	or/17-24	2994651
26	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3272772

27	25 not 26	2836173
28	6 and 16 and 27	37
29	limit 28 to yr="2017 -Current"	20

Database(s): Embase 1974 to 2023 January 09
Search date: 9 January 2023

#	Searches	Results
1	exp renal cell carcinoma/	31521
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114590
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77537
4	or/1-3	129231
5	(advanced or unresect* or un?resect* or nonresect* or (non adj2 resect*) or inopera* or unopera* or metastas* or metastat* or "end stage" or "late-stage" or "late stage" or terminal or "stage 3" or "stage iii" or "stage three" or "stage 4" or "stage iv" or "stage four").ti,ab.	2252114
6	4 and 5	51612
7	(cost? adj2 (illness or disease or sickness)).tw.	7424
8	(burden? adj2 (illness or disease? or condition? or economic*)).tw.	80797
9	("quality-adjusted life years" or "quality adjusted life years" or QALY?).tw.	28324
10	Quality-adjusted life years/	33347
11	"cost of illness"/	20913
12	exp "health care cost"/	329309
13	(out-of-pocket adj2 (payment? or expenditure? or cost? or spending or expense?)).tw.	9136
14	(expenditure? adj3 (health or direct or indirect)).tw.	13703
15	((adjusted or quality-adjusted) adj2 year?).tw.	39526
16	or/7-15	455004
17	exp United Kingdom/	454101
18	(national health service* or nhs*).ti,ab,in.	381803
19	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	56714
20	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	3527152
21	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or	2788284

	harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	
22	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	114720
23	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	384034
24	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	53264
25	or/17-24	4315463
26	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3502186
27	25 not 26	4068006
28	6 and 16 and 27	150
29	limit 28 to yr="2017 -Current"	78

Economic studies: general economic studies (including evaluations, utilities and costs) INAHTA
Search date: 10 January 2023
((("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear cell" or "non clear cell" or hypermephroma or "hypernephroid carcinoma") OR ("Carcinoma, Renal Cell"[mhe]) OR (renal AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma)) OR ((kidney AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma))) AND (economic* OR cost*) FROM 2009 TO 2023

= 137 hits

ScHCARRHUD (all searches in “any field”)
Search date: 10 January 2023
"renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear cell" or "non clear cell" or hypermephroma or "hypernephroid carcinoma"
OR
renal AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma)
OR
kidney AND (carcinoma or cancer or tumor or tumour or neoplasm or adenocarcinoma)
= 8 hits

CEA Registry (utilities)
Search date: 10 January 2023
In Abstract. Renal cell cancer or renal cell carcinoma or kidney cancer or kidney carcinoma
= 201 utilities in 46 articles (saved as CSV file)

NHS EED
Search date: 10 January 2023
"Renal cell cancer" or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma"
= 18 hits

EQ-5D
Renal cell cancer or renal cell carcinoma or kidney cancer or kidney carcinoma
= 0 hits

NICE website
Search date: 10 January 2023
"Renal cell cancer" or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma"
= 19 hits

Observational studies (to identify sources of RWE)

Database(s): Ovid MEDLINE(R) ALL 1946 to January 18, 2023
Search date: 18 January 2023

#	Searches	Results
1	exp renal cell carcinoma/	39106
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	79866
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	50806
4	or/1-3	86203
5	epidemiologic studies/	9242
6	exp case control studies/	1383274
7	exp cohort studies/	2436199
8	case control.tw.	149642
9	(cohort adj (study or studies)).tw.	298113
10	Cohort analy$.tw.	11161
11	(Follow up adj (study or studies)).tw.	55254
12	(observational adj (study or studies)).tw.	152540
13	Longitudinal.tw.	309912
14	Retrospective.tw.	710258
15	Cross sectional.tw.	487001
16	Cross-sectional studies/	453088
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	3683297
18	exp United Kingdom/	387773
19	(national health service* or nhs*).ti,ab,in.	259935
20	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	47619
21	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	2390072
22	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's"	1693813

	or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	
23	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	67988
24	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	249588
25	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	32629
26	or/18-25	2999945
27	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3275806
28	26 not 27	2841192
29	4 and 17 and 28	1251

Database(s): Embase 1974 to 2023 January 18
Search date: 18 January 2023

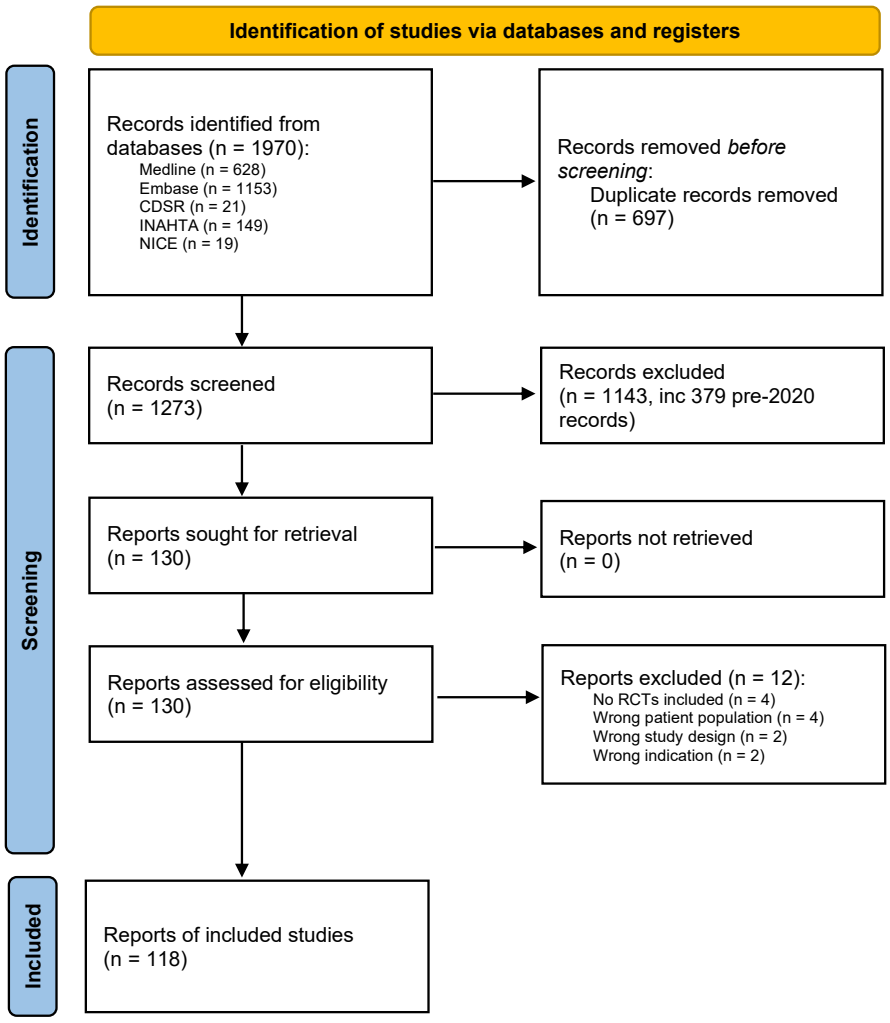
#	Searches	Results
1	exp renal cell carcinoma/	31651
2	((renal or kidney) adj3 (carcinoma or cancer* or cancer* or tumor* or tumour* or neoplas* or adenocarcinoma*)).ti,ab.	114735
3	("renal cell cancer" or RCC or "renal cell carcinoma" or "kidney cancer" or "kidney carcinoma" or "clear?cell" or "non?clear?cell" or hypermephroma or "hypernephroid carcinoma").ti,ab.	77643
4	or/1-3	129418
5	clinical study/	161553
6	case control study/	197739
7	family study/	25736

8	longitudinal study/	184564
9	retrospective study/	1369707
10	prospective study/	823747
11	randomized controlled trials/	243369
12	10 not 11	813913
13	cohort analysis/	946930
14	(Cohort adj (study or studies)).mp.	440220
15	(Case control adj (study or studies)).tw.	161491
16	(follow up adj (study or studies)).tw.	71582
17	(observational adj (study or studies)).tw.	236491
18	(epidemiologic$ adj (study or studies)).tw.	119127
19	(cross sectional adj (study or studies)).tw.	316300
20	5 or 6 or 7 or 8 or 9 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	3690630
21	exp United Kingdom/	454479
22	(national health service* or nhs*).ti,ab,in.	382750
23	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	56885
24	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	3531748
25	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or	2792236

	boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	
26	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	114888
27	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	384661
28	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	53366
29	or/21-28	4321352
30	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3508127
31	29 not 30	4073353
32	4 and 20 and 31	2210

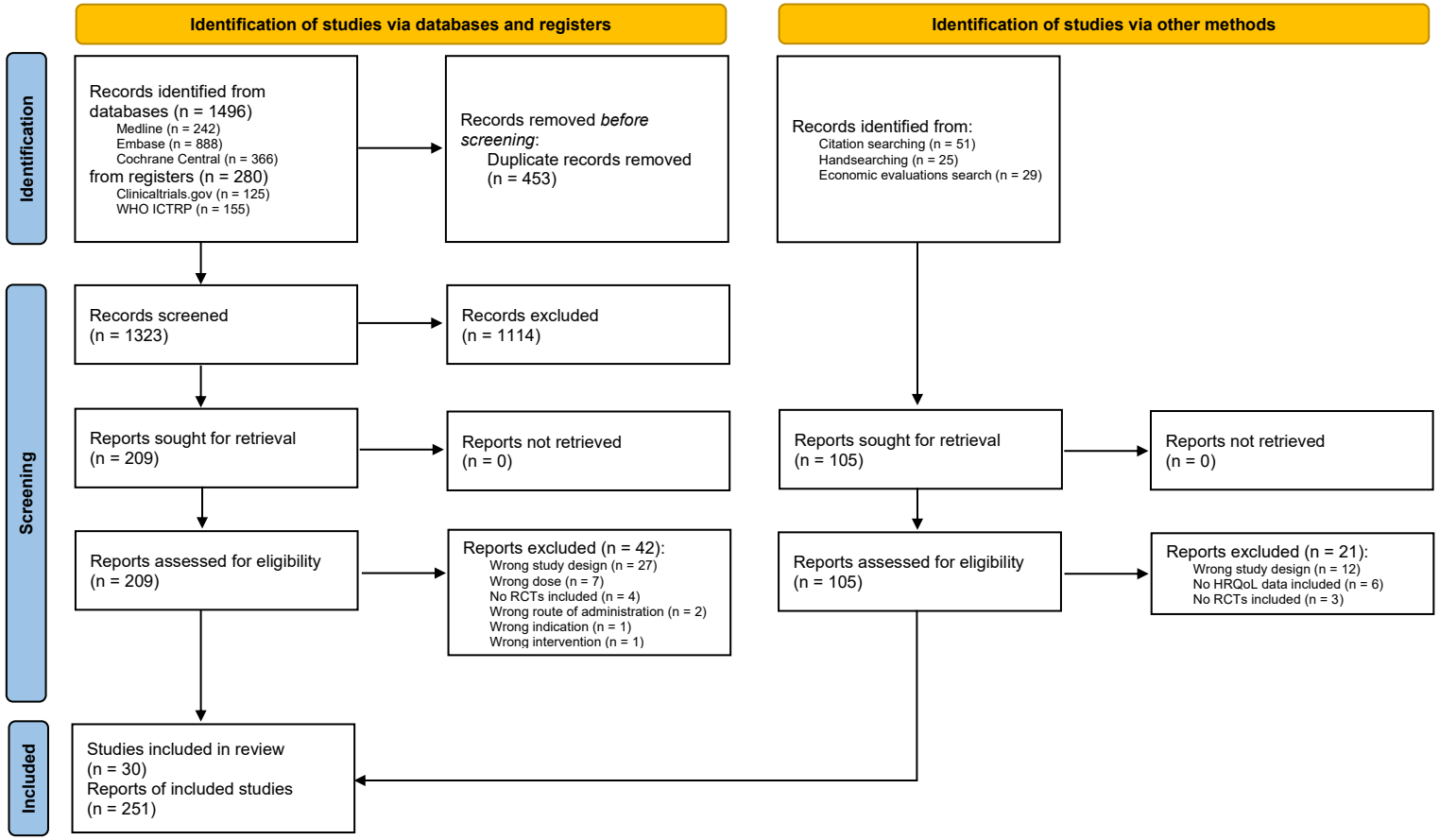
Appendix B: PRISMA diagrams for clinical review

Figure 17: Systematic reviews and meta-analyses literature review PRISMA



Abbreviations: CDSR = Cochrane Database of Systematic Reviews, INAHTA = International Network of Agencies for Health Technology Assessment, NICE = The National Institute for Health and Care Excellence; RCT = randomised controlled trials

Figure 18: RCTs literature review PRISMA



Abbreviations: WHO ICTRP = World Health Organization International Clinical Trials Registry Platform; RCTs = randomised controlled trials

Appendix C: Excluded studies

SLRs

Excluded SLRs.csv

RCTs

Excluded RCTs.csv

Economic reviews

Excluded economic studies.csv

Appendix D: Data extraction grids and quality assessment

Clinical effectiveness data extraction grid

Clinical data extraction - WORKINC

Economic reviews

Economic evaluations data extraction grid

CEA extraction_0203.xlsx

Utilities data extraction grid

Extracted utilities (Prioritised studies an

Cost and resource use data extraction grid

Cost and resource use extractions.xlsx

Quality assessment of economic evaluations

Li 2021

QUALITY ASSESSMENT FOR DECISION-ANALYTIC MODELS (CHECKLIST B FROM PHILIPS ET AL. 2004)			
Quality criterion	**Question(s)**	**Response (✓, ×, NA)**	**Comments**
S1	Is there a clear statement of the decision problem?	✓	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	✓	
	Is the primary decision maker specified?	✓	
S2	Is the perspective of the model stated clearly?	✓	
	Are the model inputs consistent with the stated perspective?	✓	Yes, data for the 6 evaluated treatments included
	Has the scope of the model been stated and justified?	×	Scope of model has been stated, but not justified.
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓	Cost, LYs, QALYs, ICER
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓	
	Are the sources of data used to develop the structure of the model specified?	✓	Rationale for selection is unclear for utility sources
	Are the causal relationships described by the model structure justified appropriately?	✓	Yes, sensitivity analysis describes the model inputs that had a disproportionate effect on the model outcome i.e. cost of sunitinib / pembrolizumab

S4	Are the structural assumptions transparent and justified?	×	Model selection not justified
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓	Broadly, however, assumption required that previous treatment has no impact on subsequent treatment effectiveness which is not explored
S5	Is there a clear definition of the options under evaluation?	✓	Yes, all listed
	Have all feasible and practical options been evaluated?	×	Paper is limited to within trial comparison for first line and rationale for choice of subsequent treatments is not completely clear
	Is there justification for the exclusion for the exclusion of feasible options?	×	Other feasible options not mentioned
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	✓	DES model could be appropriate but model selection was not justified
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	✓	Lifetime
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	×	Described but not justified
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓	Defined by line of treatment and reason for discontinuation
S9	Is the cycle length defined and justified in terms of natural history of disease?	×	Defined, not justified
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	×	Data identification methods unclear, particularly for quality of life inputs
	Where choices have been made between data sources, are these justified appropriately?	×	Some utility data comes disease areas outside of RCC which would be expected to be of limited relevance
	Has particular attention been paid to identifying data for the important parameters in the model?	×	See above

	Has the quality of the data been assessed appropriately?	NA	
	Where expert opinion has been used, are the methods described and justified?	NA	
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	✓	
D2a	Is the choice of baseline data described and justified?	✓	Used trial data and existing literature
	Are transition probabilities calculated appropriately?	×	Incomplete survival data, lack of clinical validity. Chosen by best visual fit.
	Has a half-cycle correction been applied to both cost and outcome?	×	
	If not, has this omission been justified?	×	Despite being >4 weeks no half cycle correction applied
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	×	Curve fits to trial data, relative treatment effect assumed to continue for lifetime
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	×	Documented, not justified
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	×	
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	×	No alternative fits tested
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	✓	
D2c	Are the costs incorporated into the model justified?	×	Listed, not justified
	Has the source for all costs been described?	✓	
	Have discount rates been described and justified given the target decision-maker?	✓	
D2d	Are the utilities incorporated into the model appropriate?	×	Some utilities derived from unrelated disease areas (melanoma)

	Is the source for the utility weights referenced?	✓	
	Are the methods of derivation for the utility weights justified?	×	Referenced papers, but no justification for estimation / method of derivation
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	✓	
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	✓	
	Is the process of data incorporation transparent?	✓	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	×	See comments on survival extrapolation
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	×	
D4	Have the four principal types of uncertainty been addressed?	×	PSA, OWSA, limited scenario analysis presented, no structural testing
	If not, has the omission of particular forms of uncertainty been justified?	×	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	×	Limited scenario analysis presented
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	×	
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	×	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	NA	
	If data are incorporated at point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	×	
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	✓	

C2	Are any counterintuitive results from the model explained and justified?	NA	
	If the model has been calibrated against independent data, has any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	×	

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QUALITY ASSESSMENT FOR DECISION-ANALYTIC MODELS (CHECKLIST B FROM PHILIPS ET AL. 2004)			
Quality criterion	**Question(s)**	**Response (✓, ×, NA)**	**Comments**
S1	Is there a clear statement of the decision problem?	✓	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	✓	
	Is the primary decision maker specified?	✓	
S2	Is the perspective of the model stated clearly?	✓	
	Are the model inputs consistent with the stated perspective?	✓	
	Has the scope of the model been stated and justified?	✓	
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓	
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓	3 state PartSA
	Are the sources of data used to develop the structure of the model specified?	✓	

	Are the causal relationships described by the model structure justified appropriately?	×	Independence assumption of OS and PFS not discussed
S4	Are the structural assumptions transparent and justified?	×	See above
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓	Common oncology modelling technique
S5	Is there a clear definition of the options under evaluation?	✓	
	Have all feasible and practical options been evaluated?	×	Within trial comparison
	Is there justification for the exclusion for the exclusion of feasible options?	×	No justification for exclusion of other treatments
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	✓	
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	✓	Lifetime horizon appropriate to calculate long term costs
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	×	6-week cycle not justified
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓	Yes, standard 3 state model
S9	Is the cycle length defined and justified in terms of natural history of disease?	×	6-week cycle not justified
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	×	Methods used to select utility data sources unclear
	Where choices have been made between data sources, are these justified appropriately?	NA	
	Has particular attention been paid to identifying data for the important parameters in the model?	×	Methods used to select utility data sources unclear
	Has the quality of the data been assessed appropriately?	✓	See last paragraph of discussion

	Where expert opinion has been used, are the methods described and justified?	NA	
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	✓	
D2a	Is the choice of baseline data described and justified?	✓	
	Are transition probabilities calculated appropriately?	×	Justification for extrapolation selections is not clear
	Has a half-cycle correction been applied to both cost and outcome?	✓	
	If not, has this omission been justified?	NA	
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	×	Curve fits to trial data, relative treatment effect assumed to continue for lifetime
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	×	Justification for extrapolation selections is not clear
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	×	
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	×	
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	×	
D2c	Are the costs incorporated into the model justified?	×	No justification provided but costs look standard
	Has the source for all costs been described?	✓	
	Have discount rates been described and justified given the target decision-maker?	✓	

D2d	Are the utilities incorporated into the model appropriate?	×	EQ-5D but come from different sources outside of CheckMate 9ER and selection method not justified
	Is the source for the utility weights referenced?	✓	
	Are the methods of derivation for the utility weights justified?	✓	
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	✓	
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	NA	
	Is the process of data incorporation transparent?	✓	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?		
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓	
D4	Have the four principal types of uncertainty been addressed?	×	Structural uncertainty largely unaddressed. PSA and OWSA only presented
	If not, has the omission of particular forms of uncertainty been justified?	NA	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	×	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	×	
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	×	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	✓	
	If data are incorporated at point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	NA	
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	×	No mention of model validation or testing

C2	Are any counterintuitive results from the model explained and justified?	✓	Explained impact long term follow up will have on OS data
	If the model has been calibrated against independent data, has any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	×	

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QUALITY ASSESSMENT FOR DECISION-ANALYTIC MODELS (CHECKLIST B FROM PHILIPS ET AL. 2004)			
Quality criterion	**Question(s)**	**Response (✓, ×, NA)**	**Comments**
S1	Is there a clear statement of the decision problem?	✓	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	✓	
	Is the primary decision maker specified?	✓	
S2	Is the perspective of the model stated clearly?	✓	
	Are the model inputs consistent with the stated perspective?	✓	
	Has the scope of the model been stated and justified?	✓	
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓	Costs, LYs, QALYs, ICERs
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓	Markov and 3 state PS
	Are the sources of data used to develop the structure of the model specified?	✓	Rationale for utility data selection is unclear
	Are the causal relationships described by the model structure justified appropriately?	✓	Yes, sensitivity analysis describes the model inputs that had a disproportionate effect on the model outcome i.e. cost of nivolumab / cabozantinib
S4	Are the structural assumptions transparent and justified?	✓	No mention of the fact that independence of OS and PFS is assumed in the partitioned survival model

	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓	
S5	Is there a clear definition of the options under evaluation?	✓	Yes, all listed
	Have all feasible and practical options been evaluated?	✓	Explanation for subsequent anti-cancer therapy given
	Is there justification for the exclusion for the exclusion of feasible options?	NA	
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	×	Curve selection and visual fit only
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	✓	10 year time horizon rationale explained based on 5 year survival
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓	Yes, used PFS, progressive disease, and death as the three states.
S9	Is the cycle length defined and justified in terms of natural history of disease?	✓	Yes, justification given for 1 month cycle length based off of 5 year survival rate. However, the source for this survival rate was a paper comparing nivolumab plus ipilimumab versus sunitinib.
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	×	Data identification methods unclear
	Where choices have been made between data sources, are these justified appropriately?	×	No rationale for the use of a hepatocellular carcinoma study that informed the sensitivity analysis
	Has particular attention been paid to identifying data for the important parameters in the model?	✓	
	Has the quality of the data been assessed appropriately?	✓	Yes, all listed inputs referenced
	Where expert opinion has been used, are the methods described and justified?	NA	
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	✓	
D2a	Is the choice of baseline data described and justified?	✓	Used trial data and existing literature
	Are transition probabilities calculated appropriately?	✓	Used visual inspection, Akaike information criterion and Bayesian information criterion
	Has a half-cycle correction been applied to both cost and outcome?	×	Estimation for probabilities and proportions of curves not clearly explained

	If not, has this omission been justified?	×	
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	✓	
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	×	No, estimation for Kaplan Meier curves derived from method described in paper that evaluated temsirolimus
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	✓	Explored, but estimation methods not justified
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	✓	
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	×	
D2c	Are the costs incorporated into the model justified?	✓	Used same KM curves from Sunitinib group for whole population due to lack of data
	Has the source for all costs been described?	✓	Yes, all listed
	Have discount rates been described and justified given the target decision-maker?	✓	
D2d	Are the utilities incorporated into the model appropriate?	✓	Yes, all studies used are within same disease area, and all evaluated nivolumab plus cabozantinib and sunitinib
	Is the source for the utility weights referenced?	✓	Referenced two papers as sources for utility weight
	Are the methods of derivation for the utility weights justified?	×	Stated not justified
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	✓	
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	×	Not explained why hepatocellular carcinoma study was used in sensitivity analysis
	Is the process of data incorporation transparent?	✓	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	✓	
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓	Monte Carlo simulation used to reflect second order uncertainty
D4	Have the four principal types of uncertainty been addressed?	×	Heterogeneity not addressed

	If not, has the omission of particular forms of uncertainty been justified?	NA	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✓	Ran OWSA/TWSA and probabilistic sensitivity analysis with different model parameters e.g. cost
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	✓	Yes, see above
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	×	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	×	No rationale for arbitrary use of "± 20% from the baseline" for parameter estimates in sensitivity analysis
	If data are incorporated at point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	×	See above. Ranges not justified
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	✓	
C2	Are any counterintuitive results from the model explained and justified?	✓	Explained problems related to assumed utilities adopted in the model
	If the model has been calibrated against independent data, has any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	×	No comparison to previous models

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QUALITY ASSESSMENT FOR DECISION-ANALYTIC MODELS (CHECKLIST B FROM PHILIPS ET AL. 2004)			
Quality criterion	**Question(s)**	**Response (✓, ×, NA)**	**Comments**
S1	Is there a clear statement of the decision problem?	✓·	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	✓·	
	Is the primary decision maker specified?	✓·	
S2	Is the perspective of the model stated clearly?	✓·	

	Are the model inputs consistent with the stated perspective?	✓·	Clinical inputs from CM9ER trial. Utility inputs from Chinese indexes and RMB currency was calculated.
	Has the scope of the model been stated and justified?	×·	Scope of model not justified, but scope is stated clearly.
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓·	Costs, LYs, QALYs, and ICERs. Comparing nivolumab plus cabozantinib and sunitinib
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓·	Yes, 3 state PS models are commonly used to evaluate oncology therapies
	Are the sources of data used to develop the structure of the model specified?	✓·	
	Are the causal relationships described by the model structure justified appropriately?	✓·	Yes, second half of discussion justifies the relationships described by the model
S4	Are the structural assumptions transparent and justified?	×·	No mention of the assumption that OS and PFS are independent in the PS model
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓·	
S5	Is there a clear definition of the options under evaluation?	✓·	Yes, all listed
	Have all feasible and practical options been evaluated?	×·	Limited to in trial comparison of first line treatments
	Is there justification for the exclusion for the exclusion of feasible options?	×·	
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	✓·	Standard three state partitioned survival model used
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	✓·	Yes, 20-year survival model used, although no justification
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	×·	Cycle and time horizon stated but not justified
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓·	
S9	Is the cycle length defined and justified in terms of natural history of disease?	✓··	6-week cycle length used
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	✓·	**Yes,** stated where European or US data was used / extrapolated
	Where choices have been made between data sources, are these justified appropriately?	✓·	See above

	Has particular attention been paid to identifying data for the important parameters in the model?	✓·	
	Has the quality of the data been assessed appropriately?	✓·	
	Where expert opinion has been used, are the methods described and justified?	NA	
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	✓·	
D2a	Is the choice of baseline data described and justified?	✓·	**Used trial data and existing literature**
	Are transition probabilities calculated appropriately?	×·	Model selection appropriate, but survival data incomplete. Lacks clinical validity. Based on statistical fit
	Has a half-cycle correction been applied to both cost and outcome?	×·	
	If not, has this omission been justified?	×·	Lack of half cycle correction has not been justified, despite cycle being 6 weeks long
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	✓·	
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	✓·	Used Royston/Parmer spline and non-mixture cure models to avoid underestimation that occurs in traditional models
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	✓·	
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	✓·	Used nine models to fit, and compared with KM curves from extrapolated survival curves
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	×·	
D2c	Are the costs incorporated into the model justified?	×·	Lack of cost justification, although assumptions described.
	Has the source for all costs been described?	✓·	Yes, all listed
	Have discount rates been described and justified given the target decision-maker?	✓·	

D2d	Are the utilities incorporated into the model appropriate?	✓·	
	Is the source for the utility weights referenced?	✓·	
	Are the methods of derivation for the utility weights justified?	×·	Not justified, utility sources described.
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	✓·	
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	×·	Patient weight assumed to be 65kg, but not justified. Willingness to pay threshold was assumed to be 3x GDP per capita, but not justified.
	Is the process of data incorporation transparent	✓··	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	✓·	All distributions are described for each parameter but not justified
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓··	Monte Carlo simulation used to reflect second order uncertainty
D4	Have the four principal types of uncertainty been addressed?	✓·	Yes, although not specifically stated
	If not, has the omission of particular forms of uncertainty been justified?	×·	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✓·	Yes, used different treatment scenarios
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	✓·	The effect of structural uncertainties addressed in sensitivity analysis
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	✓·	Effect of discount rates assessed
D4d	Are the methods of assessment of parameter uncertainty appropriate?	✓·	Probabilistic sensitivity analysis plus a series of one-way sensitivity analyses
	If data are incorporated at point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	NA	
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	✓·	
C2	Are any counterintuitive results from the model explained and justified?	×·	
	If the model has been calibrated against independent data, has any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	×·	No related studies listed

Appendix E: Network diagrams

network plots 110423.docx