

**LIVERPOOL REVIEWS AND
IMPLEMENTATION GROUP (LRiG)**

**Lenvatinib with pembrolizumab
for untreated advanced renal cell
carcinoma [ID3760]**

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Abbreviations

AG	Assessment Group
ASCO	American Society of Clinical Oncology
CRD	Centre for Reviews and Dissemination
EMA	European Medicines Agency
FDA	US Food and Drug Administration
HTA	Health technology assessment
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
LRiG	Liverpool Reviews and Implementation Group
LY	Life year
MHRA	Medicines and Healthcare products Regulatory Agency
MSKCC	Memorial Sloan Kettering Cancer Center
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
QALY	Quality adjusted life year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial

1 Title of the project

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

2 Name of TAR team and 'lead'

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3 Plain English summary

Renal cell carcinoma is a cancer affecting the lining of small tubes in the kidneys. This type of cancer often forms without patients having any symptoms and around 50% of all patients have cancer that has spread beyond the kidneys. This group of patients can be treated with either a single drug or, in some cases, two drugs given together. We will review how well a new combination of drugs (lenvatinib plus pembrolizumab) works. We will also explore the value for money of this new treatment combination compared with other treatments used to treat NHS patients.

4 Decision problem

4.1 Purpose of the decision to be made

The remit of this review is to appraise the clinical and cost effectiveness of lenvatinib in combination with pembrolizumab (lenvatinib+pembrolizumab) within its European Medicines Agency (EMA) marketing authorisation for the treatment of untreated advanced renal cell carcinoma (RCC).

4.2 Background

4.2.1 The disease

Renal cell carcinoma (RCC) is a type of kidney cancer arising from the renal parenchyma/cortex whereby malignant cells form in tubules of the kidney. Risk factors for RCC include smoking, obesity, hypertension and acquired cystic kidney disease.¹⁻³

RCC has a number of histological subtypes,⁴ the most common being clear cell RCC, which is reported to account for between 70% and 90% of all cases of RCC.^{1-3,5} Non-clear cell RCC is a heterogeneous group of kidney cancers with distinct histologies, diverse biologic behaviours and different clinical outcomes.^{6,7}

Patients with RCC are often asymptomatic and >50% of patients are diagnosed incidentally.^{1,2} At diagnosis, RCC is categorised into four stages of disease. Stages 1 and 2 denote early-stage disease and Stages 3 and 4 denote advanced-stage disease.^{1,2,8} Patients with Stage 1 and Stage 2 disease have RCC where the tumour is confined to the kidney, the difference between the two stages is the size of the tumour. A patient is diagnosed with Stage 3 (locally advanced) disease when the tumour is growing into a major vein or has spread to regional lymph nodes. A patient is diagnosed with Stage 4 (metastatic) disease when the tumour is growing into the adrenal gland on top of the kidney or has spread to distant lymph nodes and/or other organs.

4.2.2 Epidemiology

In 2015-2017, there were 19,973 new cases of kidney cancer in the UK (England: 10,759; Wales: 631).⁹ Worldwide, kidney cancer is twice as common in men than women.³ In the UK, in 2015-2017, there were 1.7 times more cases in men than women.⁹ A quarter of cases were diagnosed in people aged 60 to 69 years, with nearly half of cases (49%) diagnosed in people aged 70 years and over. RCC is the most common type of kidney cancer, comprising approximately 85% of all renal malignancies.^{3,5}

Between 2013 and 2017, 43.0% of all cases of kidney cancer with a known stage of diagnosis in England were classified as being advanced stage cancers (Table 1). The 5-year relative

survival rates by stage of disease were markedly lower for patients with Stage 4 (metastatic) disease than the other stages of kidney cancer (Table 1).

Table 1 Proportion of people diagnosed with kidney cancer by stage and 5-year survival (England, 2013-2017)

Disease stage	Number diagnosed	Proportion diagnosed	Proportion with known diagnosis	Proportion alive after 5years
Unknown	7112	16.2%	n/a	n/a
Stage 1	17,708	40.2%	48.0%	86.8%
Stage 2	3346	7.6%	9.1%	76.6%
Stage 3	6829	15.5%	18.5%	74.2%
Stage 4	9024	20.5%	24.5%	12.4%
All	44,019	100.0%	100.0%	63.8%

n/a=not applicable

Source: Public Health England – National Cancer Registration and Analysis Service, Office for National Statistics¹⁰

4.2.3 Current treatment options

For patients with early RCC and locally advanced RCC, surgery is usually possible and is the preferred treatment. However, surgery is rarely a treatment option for patients with metastatic RCC. Surgery is usually curative. However, results from two studies^{11,12} that have explored disease progression following surgery suggest that approximately 30% of patients subsequently develop metastatic RCC.

In NHS clinical practice, standard first-line drug treatments for advanced RCC are in line with NICE guidance (Table 2). Currently, NICE recommended treatments are restricted to monotherapy with systemic vascular endothelial growth factor receptor (VEGFR)-targeted tyrosine-kinase inhibitor (TKI) agents (sunitinib,¹³ pazopanib,¹⁴ tivozanib¹⁵ and cabozantinib¹⁶). However, two combination therapies are currently available via the Cancer Drugs Fund: avelumab+axitinib¹⁷ (an immunotherapy in combination with a VEGFR-TKI) and nivolumab+ipilimumab¹⁸ (immunotherapy drugs). Other treatment options, which are now rarely used due to their associated toxicities include interferon alpha (IFN- α) and high-dose interleukin-2 (IL-2).¹

As shown in Table 2, two of the treatment options (cabozantinib and nivolumab+ipilimumab) are only available to patients with intermediate or poor risk status according to International Metastatic RCC Database (IMDC) criteria.¹⁹ The IMDC criteria categorise patients as having favourable, intermediate or poor risk based on how many adverse prognostic factors are present. Another classification system that has been used to identify risk is the Memorial Sloan Kettering Cancer Center (MSKCC) risk stratification model.²⁰ Both the IMDC and MSKCC models calculate risk by assessing time from diagnosis to systemic treatment, haemoglobin levels, calcium levels and Karnofsky performance status (KPS). In addition, the MSKCC model includes levels of lactate dehydrogenase as a prognostic risk factor, whereas the IMDC model

considers absolute neutrophil count and platelet count as additional prognostic factors. For both risk scoring systems, a patient is considered to be at favourable risk if none of the adverse prognostic risk factors are present, at intermediate risk if less than three adverse prognostic risk factors are present and at poor risk if three or more adverse prognostic risk factors are present. Heng et al 2013²¹ reported that the IMDC and MSKCC models were concordant; 83% of patients were classified into the same risk group by each model. A retrospective analysis of the Czech Patient Registry RENal Information System²² found the proportion of patients with intermediate risk status to be similar (IMDC: 62%; MSKCC: 61%); however, the IMDC model classified more patients as favourable risk and fewer as poor risk.

Table 2 Previous NICE appraisals of first-line treatments for advanced RCC

NICE TA	Intervention(s)	NICE recommendation
TA169 (2009) ¹³	Sunitinib	Sunitinib is recommended a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG PS of 0 or 1.
TA178 (2009) ^{23*}	Bevacizumab Sorafenib Temsirolimus	Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic RCC.
TA215 (2011 / 2013) ¹⁴	Pazopanib	Pazopanib is recommended as a first-line treatment option for people with advanced RCC who have not received prior cytokine therapy and have an ECOG PS of 0 or 1.
TA512 (2018) ¹⁵	Tivozanib	Tivozanib is recommended for treating advanced RCC in adults who have had no previous treatment, only if the company provides tivozanib with the discount stated in the Patient Access Scheme agreement.
TA542 (2018) ¹³	Cabozantinib	Cabozantinib is recommended, within its marketing authorisation, for adults with untreated advanced RCC that is intermediate- or poor-risk as defined by the IMDC criteria. It is recommended only if the company provides cabozantinib according to the commercial arrangement.
TA581 (2019) ¹⁸	Nivolumab+ipilimumab	Nivolumab with ipilimumab is recommended for use within the Cancer Drugs Fund as an option for adults with untreated advanced RCC that is intermediate- or poor-risk as defined in the IMDC criteria. It is recommended only if the conditions in the managed access agreement for nivolumab with ipilimumab are followed.
TA645 (2020) ¹⁷	Avelumab+axitinib	Avelumab with axitinib is recommended for use within the Cancer Drugs Fund as an option for untreated advanced RCC in adults. It is recommended only if the conditions in the managed access agreement for avelumab with axitinib are followed.
TA650 (2020) ²⁴	Pembrolizumab+axitinib	Pembrolizumab with axitinib is not recommended, within its marketing authorisation, for untreated advanced RCC in adults.

*Also considered sorafenib and sunitinib as second-line treatments as part of this appraisal, neither of which were recommended
ECOG PS=Eastern Cooperative Oncology Group performance status; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; RCC=renal cell carcinoma; TA=technology appraisal

4.3 Clear definition of the intervention

Lenvatinib (Kisplyx, Eisai) is an oral VEGFR-TKI agent that selectively inhibits VEGFRs and other receptor tyrosine kinases that are involved in the growth of blood vessels to the tumour and tumour proliferation. Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised monoclonal antibody that is administered intravenously in order to target and block the

programmed death 1 (PD-1) receptor with the aim of promoting an anti-tumour immune response.

Lenvatinib with pembrolizumab does not currently have a marketing authorisation in the UK for untreated advanced RCC. It is, however, authorised by the United States (US) Food and Drug Administration (FDA)²⁵ for first-line treatment of adult patients with advanced RCC. Randomised controlled trial (RCT) evidence considered by the FDA was derived from the Phase III CLEAR trial²⁶ of adults with untreated advanced RCC. In this trial, lenvatinib was administered orally at a dose of 20mg once daily. Pembrolizumab was administered intravenously at a dose of 200mg every 3 weeks.

According to information provided by the companies to NICE, the key timelines for UK licensing are as follows:

- CHMP positive opinion is anticipated in [REDACTED].
- UK approval from the Medicines and Healthcare products Regulatory Agency (MHRA) and EMA is anticipated in [REDACTED].
- UK launch of the technology is anticipated in [REDACTED].

4.4 Relevant comparators

Relevant comparators to lenvatinib+pembrolizumab are the four first-line treatments recommended by NICE¹³⁻¹⁶ namely:

- pazopanib
- sunitinib
- tivozanib
- cabozantinib (only for intermediate- or poor-risk disease as defined in IMDC criteria).¹⁹

The combination treatment of nivolumab+ipilimumab²⁷ is currently subject to an ongoing CDF review as a treatment option for patients with intermediate- or poor-risk disease (as defined in the IMDC criteria). Nivolumab+ipilimumab will be considered a relevant comparator if recommended by NICE.

Although avelumab+axitinib¹⁷ is also available to NHS patients via the CDF, it is not currently subject to CDF review and is therefore not a relevant comparator, in line with NICE policy and procedures.²⁸

4.5 Population and relevant subgroups

The population of interest is patients with untreated advanced RCC. If data allow, relevant subgroups will include patients categorised by IMDC risk status.

4.6 Outcomes to be addressed

If data allow, outcome measures will include:

- overall survival (OS)
- progression-free survival (PFS)
- response rates (objective response rate, clinical benefit rate and disease control rate)
- adverse effects of treatment
- health-related quality of life (HRQoL)
- cost effectiveness

4.7 Key factors to consider

It has been noted by the ERG and NICE Appraisal Committee (AC) in previous appraisals^{17,18} that there is a lack of evidence to guide treatment for patients with non-clear cell RCC. This is primarily due to non-clear cell RCC being (i) heterogeneous (up to 15 subtypes are listed in the most recent World Health Organisation classification of RCC⁶) and (ii) less common^{6,7} than clear cell RCC. Most RCTs either only include patients with clear cell RCC or a small proportion of patients with non-clear cell RCC. Due to the lack of evidence available for patients with non-clear cell RCC, it is difficult to draw any specific conclusions for this group of patients. The Assessment Group (AG) analyses will focus on the evidence available.

When considering subgroup analyses based on risk status, the IMDC classification¹⁹ will be preferred since this is what is used in NHS clinical practice and is specified in final NICE scope.²⁹ Where risk status has only been assessed using the MSKCC classification,²⁰ this will be used instead. The subgroup based on risk status specified in the final NICE scope²⁹ is intermediate/poor risk status. NHS patients classified as having intermediate or poor risks are also potentially eligible for first-line treatment with cabozantinib¹⁶ or nivolumab+ipilimumab (through the CDF).¹⁸ However, since risk is identified as a prognostic factor, and since poor risk patients by definition have more risk factors than intermediate risk patients, if the data allow, it will also be informative to consider the data for intermediate and poor risk groups separately.

Previous NICE ACs¹⁵⁻¹⁸ have concluded that sunitinib and pazopanib are of equivalent clinical effectiveness and that: “At best, tivozanib may have a similar effect to sunitinib or pazopanib.”¹⁵ The AG will explore whether tivozanib can be considered to have equivalent clinical effectiveness as sunitinib and pazopanib.

5 Report methods for synthesis of evidence of clinical effectiveness

A systematic review of clinical effectiveness evidence will be undertaken following the general principles outlined by the Centre for Reviews and Dissemination (CRD)³⁰ and reported using the criteria recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.³¹ Searches will be conducted in accordance with the general principles recommended by the European network for Health Technology Assessment.³² The protocol details will be submitted for registration on PROSPERO, an international database of prospectively registered systematic reviews in health and social care.³³

5.1 Search strategy

The AG will identify clinical effectiveness studies by searching major medical databases including MEDLINE, EMBASE, PubMed, the Cochrane Library (CENTRAL) and the International Network of Agencies for Health Technology Assessment's International Health Technology Assessment Database. The clinical effectiveness search strategy will be designed to identify RCTs for inclusion in the clinical effectiveness review. In addition, abstracts of studies reported at relevant conferences (proceedings from American Society of Clinical Oncology [ASCO], ASCO-Genitourinary [ASGO-GU], European Society for Medical Oncology [ESMO], European Conference for Clinical Oncology [ECCO]) and Health Technology Assessment International [HTAi]) held between 2019 and 2021. Information on studies in progress will be identified through searching a range of relevant databases including clinicaltrials.gov, International Clinical Trials Registry Platform and European Union Clinical Trials Register.

Attempts to identify any relevant studies not identified by electronic searches will be made by contacting the AG's clinical experts and examining the reference lists of all included articles. In addition, the following grey literature sources will be assessed for relevant data and/or unpublished data: company submissions for this current appraisal,²⁹ company submissions for previous relevant NICE appraisals (TA169,¹³ TA178,²³ TA215,¹⁴ TA512,¹⁵ TA542,¹⁶ TA581,¹⁸ TA650,²⁴ TA645,¹⁷) and regulatory reports (for example, Scottish Medicines Consortium [SMC], Canadian Agency for Drugs and Technologies in Health [CADTH], Haute Autorité de Santé [HAS]) Pharmaceutical Benefits Advisory Committee [PBAC], EMA, MHRA and FDA). Citation searches of included articles will also be undertaken.

A database of published literature will be assembled from the aforementioned sources, collated in a bibliographic database (Endnote X9 software package³⁴) and exported to a specialist systematic review management system (Covidence systematic review software³⁵).

More information in relation to the searches is provided in Appendix 1 (Section 10.1), including an example of the MEDLINE draft search strategy (Section 10.1.1). Full details of the search process will be presented in the final report.

5.2 Inclusion and exclusion criteria

Two reviewers will independently screen all titles and abstracts identified in the initial searches. Full text copies of any titles/abstracts that may be eligible for inclusion will be obtained and assessed for inclusion by two reviewers using the inclusion criteria listed in Table 3. Conference abstracts will be included where sufficient methodological details are reported to allow critical appraisal of study quality. Any discrepancies will be resolved through consultation with a third reviewer. Publications that do not meet the inclusion criteria will be excluded and their bibliographic details listed with reasons for exclusion.

Table 3 Inclusion and exclusion criteria for clinical effectiveness evidence

Criteria	Inclusion	Exclusion
Patient population	<ul style="list-style-type: none"> Patients with untreated advanced RCC. If a study includes a mixed population and provides subgroup analysis results for the population with untreated advanced RCC, then this study will be included in the review 	<ul style="list-style-type: none"> Publications which do not include analyses of patients with untreated advanced renal cell carcinoma
Intervention	<ul style="list-style-type: none"> Lenvatinib+pembrolizumab for previously untreated advanced renal cell carcinoma 	<ul style="list-style-type: none"> Lenvatinib monotherapy Pembrolizumab monotherapy
Comparators	<ul style="list-style-type: none"> Pazopanib Sunitinib Tivozanib Cabozantinib (only for intermediate- or poor-risk disease as defined by IMDC criteria^b) Nivolumab+ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) – subject to ongoing CDF review^c 	<ul style="list-style-type: none"> Avelumab+axitinib^a Any other treatment that is not recommended by NICE for patients with untreated advanced RCC
Outcomes	<ul style="list-style-type: none"> Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life 	<ul style="list-style-type: none"> Publications will not be excluded based on outcomes reported
Study design	<ul style="list-style-type: none"> RCTs 	<ul style="list-style-type: none"> Non-RCTs
Limits	<ul style="list-style-type: none"> English language 	<ul style="list-style-type: none"> Not English language

^a Avelumab+axitinib is only available to NHS patients via the Cancer Drugs Fund (CDF);¹⁷ it is not subject to an ongoing CDF review, and therefore is not a relevant comparator²⁸

^b Cabozantinib is only recommended by NICE¹⁶ for intermediate- or poor- risk disease as defined in the IMDC criteria

^c Nivolumab+ipilimumab is only recommended by NICE¹⁸ for intermediate or poor risk disease as defined in the IMDC criteria; it is currently only available to NHS patients via the CDF but is currently subject to an ongoing CDF review²⁷

CDF=Cancer Drugs Fund; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; RCC=renal cell carcinoma; RCT=randomised controlled trial

5.3 Data extraction and quality assessment strategy

Using a standardised data extraction form, data relating to study and population characteristics and outcomes will be extracted by one reviewer and independently checked for accuracy by a second reviewer. See Appendix 2 (Section 10.2.1) for an example of the type of data to be included. Disagreement will be resolved through consensus, and, if necessary, a third reviewer will be consulted. Time permitting, study authors will be contacted and asked to provide missing data. Data from multiple publications will be extracted and reported as a single study.

The quality of the RCTs will be assessed according to criteria published in the CRD's Guidance for undertaking reviews in healthcare.³⁰ The quality of the included studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted.

5.4 Data analysis/synthesis

The results of the data extraction and quality assessment for each included study will be presented in structured tables and as a narrative summary. Studies will be grouped according to comparators. The possible effects of study quality on the effectiveness data and review findings will be discussed. Treatment effect estimates and corresponding 95% confidence intervals will be extracted from the full text papers or calculated from presented data if sufficient data are available.

Treatment effect estimates will be presented as hazard ratios (HRs) for time-to-event data, relative risks for dichotomous data, or as mean differences for continuous data.

Clinical and methodological heterogeneity between the included studies will be assessed by considering differences in (a) study population, (b) interventions, (c) outcome measures, and (d) study quality. In addition, if pooling two or more studies including the same treatments in meta-analysis is possible and clinically meaningful, forest plots will be visually assessed for the presence of heterogeneity. The Chi-squared test will be performed ($p < 0.1$) and the I^2 statistic will be calculated to quantify statistical heterogeneity.

If direct comparisons with all relevant comparators are not possible then, if the data allow, indirect treatment comparisons will be conducted. Where appropriate, indirect comparisons will be considered for all outcomes. The AG will assess the feasibility of performing an indirect comparison by evaluating:

- 1) the clinical and methodological heterogeneity of the included studies with regard to (a) study population, (b) interventions and comparators, (c) outcome measures, and (d) study quality and

- 2) the feasibility of constructing a suitable, connected network of treatments relevant to the decision problem for each outcome.

Preferably, the AG will include only RCTs of treatments relevant to the decision problem within the network (i.e., network nodes of lenvatinib+pembrolizumab, pazopanib, sunitinib, tivozanib, cabozantinib and nivolumab+ipilimumab). However, if a suitable, connected network of all relevant treatments cannot be constructed, the AG will consider including additional treatments (i.e., nodes) within the network to form connections.

If the AG determines that indirect comparisons are feasible, NMAs will be performed in a Bayesian framework using R software (e.g., using the *multinma* R package³⁶) or WinBUGS software.³⁷ Network Meta-Analyses (NMAs) conducted by the AG will follow the guidance provided in Decision Support Unit (DSU) documents 2, 3 and 4.³⁸⁻⁴⁰

NMAs will be performed using fixed-effects (FE) and random-effects (RE) models. Results of both FE and RE models will be presented; the AG will select the most appropriate approach to modelling (FE or RE) based on the presence of clinical and statistical heterogeneity between included RCTs. In the absence of any important clinical or statistical heterogeneity between included RCTs, best fitting models will be selected according to model fit statistics (i.e., Deviance Information Criteria and posterior Residual Deviance).

If at least one closed loop is present within the network for each outcome, inconsistency in the NMAs will be assessed by applying an inconsistency model (e.g., an unrelated mean effects model⁴⁰) and by comparing model fit statistics of inconsistency models with consistency models.

The outputs from the NMAs will be the estimated treatment effects for each treatment relative to every other treatment included in the network; treatment effect estimates will be presented as HRs for time-to-event data (i.e., OS and PFS), relative risks (RRs) for dichotomous data (i.e., response rate and adverse effects), or as mean differences (MDs) for continuous data (i.e., HRQoL) with 95% credible intervals.

For time-to-event outcomes (i.e., OS and PFS) presented as HRs, the AG will assess the validity of the proportional hazards (PH) assumption for all RCT outcomes included in the NMAs using figures (e.g., Schoenfeld residuals plots or log cumulative hazard plots) and statistical tests (e.g., Grambsch-Therneau test⁴¹) presented within company submissions for lenvatinib+pembrolizumab and for relevant comparators, where available. If insufficient information is provided within the company submissions to assess PH, the AG will produce

Schoenfeld residuals plots and perform Grambsch-Therneau test using Kaplan-Meier (K-M) data included within company submissions or by digitising K-M data, where possible.

In the event that the PH assumption is violated for OS or PFS within one or more of the RCTs included in the NMAs, the AG will consider using NMA modelling approaches for time-varying HRs.^{42,43}

If the evidence allows, the AG will perform NMAs for subgroups of patients by disease risk as defined by the IMDC criteria. If the AG identifies important sources of clinical and methodological heterogeneity of the included studies with regards to (a) study population, (b) interventions and comparators, (c) outcome measures, and (d) study quality, the AG will also consider performing further subgroup or sensitivity analyses to examine the impact of the clinical or methodological heterogeneity on NMA results.

6 Report methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost studies

The purpose of the economic systematic literature review is to identify published economic evaluations of lenvatinib+pembrolizumab for untreated advanced RCC, and to source published estimates to use as parameter values (e.g., resource use, costs and utilities) in any de novo economic modelling conducted by the AG.

6.2 Search strategy

Economic filters will be applied instead of the RCT filter to the electronic database search strategy (previously described in Section 5) to identify cost effectiveness evidence. In addition to the clinical databases listed in Section 5, NHS Economic Evaluation Database (EED), EconLit and Cost Effectiveness Analysis Registry will also be searched. All electronic databases will be searched from 2006, as scoping searches revealed no relevant economic evaluations prior to this date, likely due to the recent introduction of lenvatinib.

In addition to searches of ASCO, ASGO-GU, ESMO, ECCO and HTAi, the AG will also search the abstracts of studies reported at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conference between 2019 and 2021. The same grey literature sources used to identify clinical effectiveness evidence will be searched to identify cost effectiveness evidence.

A database of published literature will be assembled from the aforementioned sources, collated in a bibliographic database (Endnote X9 software package³⁴) and exported to a specialist systematic review management system (Covidence systematic review software³⁵).

More information in relation to the searches is presented in Appendix 1 (Section 10.1), including an example of the MEDLINE draft search strategy (Section 10.1.2). Full details of the search process will be presented in the final report.

6.3 Inclusion and exclusion criteria

6.3.1 Cost effectiveness studies

In addition to the population, intervention, comparator inclusion and exclusion criteria described in Table 3, the criteria listed in Table 4 will be applied.

Table 4 Inclusion and exclusion criteria for cost effectiveness evidence

Criteria	Inclusion	Exclusion
Study design	Full economic evaluations that consider both costs and consequences (cost effectiveness analysis, cost utility analysis, cost minimisation analysis and cost benefit analysis)	Partial economic evaluations that only consider either costs or consequences or do not compare two or more treatments with each other
Outcomes	Incremental cost per LY gained and/or incremental cost per QALY gained	Non-incremental outcomes or incremental outcomes that are not LYs or QALYs

LY=life year; QALY=quality adjusted life year

Only full economic evaluations that compare two or more treatments and consider both costs and consequences (including cost effectiveness, cost utility and cost benefit analyses) will be included in the AG's systematic review. If any economic evaluations are presented in the company submissions, these will be included in the review. Studies that do not meet all of the criteria will be excluded and reasons for exclusion, along with bibliographic details, will be provided.

6.3.2 Data extraction

Using a standardised data extraction form (see Appendix 2 [Section 10.2.2]) for an example of the type of data to be included), study characteristics and outcome data will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus and, if necessary, a third reviewer will be consulted. Time permitting, study authors will be contacted and asked to provide missing data. Data from multiple publications will be extracted and reported as a single study.

6.3.3 Quality assessment

The quality of the individual cost effectiveness studies will be assessed by one reviewer and independently checked for agreement by a second reviewer. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of the reported cost effectiveness studies/models will be assessed according to the CHEERS checklist.⁴⁴ This checklist reflects the criteria for economic evaluation detailed in the Guide to the Methods of Technology Appraisal developed by NICE.⁴⁵

Extracted data and quality assessment results will be presented in structured tables and as narrative descriptions. The potential effects of study quality on study results and review findings will be discussed.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the company/sponsor submission(s) to NICE, will be collated and presented within the AG report, as appropriate.

6.4 Health economic modelling

6.4.1 Model structure

The AG will critically appraise the economic models submitted by the companies and will either adapt one of these models or build a de novo economic model to generate cost effectiveness results. The AG's model will be constructed in Microsoft Excel and conform to the NICE Reference Case.⁴⁵ The AG's model is anticipated to be a partitioned survival model; this choice of model structure is in line with the modelling that has been used to inform previous NICE appraisals¹³⁻¹⁵ of untreated advanced RCC.

6.4.2 Clinical effectiveness data

For the comparison of lenvatinib+pembrolizumab versus sunitinib for patients with untreated advanced RCC, the AG considers that the CLEAR trial²⁶ is the most appropriate source of treatment effectiveness data; it is anticipated that PFS, OS and adverse event estimates from this trial will be used in the AG's model. For the comparison of lenvatinib+pembrolizumab versus the other comparators listed in the final scope²⁹ issued by NICE, treatment effectiveness estimates will be derived from the indirect comparisons carried out by the company and/or the AG.

Validation of the treatment pathways and clinical parameters used in the AG's model will be obtained through discussion with the AG's clinical advisors.

6.4.3 Cost data

The primary perspective for the analysis of cost information will be that of the UK NHS. Where possible, the Personal Social Services perspective will also be considered. Cost data collection will focus on the marginal direct health service costs associated with the interventions. The relevant time horizon for the analysis will be a patient's lifetime. In line with guidance presented in the Guide to the Methods of Technology Appraisal,⁴⁵ the costs of generic drugs will be taken from sources that reflect nationally available prices (e.g., the British National Formulary⁴⁶ and the NHS Electronic Marketing Information Tool [eMIT]⁴⁷).

Quantities of resources will be identified via consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g., Personal Social Services Research Unit⁴⁸) or obtained from other relevant sources (e.g., drug price lists, NHS Reference Costs⁴⁹).

For lenvatinib+pembrolizumab and sunitinib, time on treatment data from the CLEAR trial²⁶ will be used to estimate treatment costs. For other relevant comparators, time on treatment will be estimated in line with the conditions of use set out in the relevant NICE guidance and/or EMA licence for each treatment.

Where appropriate, costs will be discounted at 3.5% per annum, the rate recommended in the Guide to the Methods of Technology Appraisal⁴⁵ for companies and sponsors of submissions.

Cost effectiveness results using the list prices of all drugs will be used in the AG's base case analysis. The AG will also produce a confidential appendix which will include cost effectiveness results using any agreed Commercial Access Agreements (CAA) or Patient Access Schemes (PAS) prices of the intervention or comparator drugs.

6.4.4 Assessment of benefits

The AG anticipates that the main measure of benefit considered in the economic analysis will be quality adjusted life years (QALYs). To estimate QALYs, EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) values collected from patients in the CLEAR trial²⁶ will be used in the AG's base case analysis.

Where appropriate, effectiveness and other measures of benefit will be discounted at 3.5% per annum, the rate recommended in the Guide to the Methods of Technology Appraisal⁴⁵ for companies and sponsors of submissions.

6.4.5 Sensitivity and scenario analysis

Sensitivity analyses

Sensitivity analyses will be carried out to assess the robustness of the AG's base case cost effectiveness results to realistic variations in the levels of the underlying parameter values.

For deterministic sensitivity analyses, parameters will be varied around the confidence intervals/credible intervals for each parameter where available, or by $\pm 25\%$ of the base case value if estimates of variance for the parameter are not available.

Probabilistic sensitivity analysis will be performed using distributions drawn from trial or published sources where available, or assumed where not available, for all key model parameters.

Scenario analyses

The AG will conduct searches of published evidence, focussing on previous NICE appraisals in this disease area (TA169,¹³ TA178,²³ TA215,¹⁴ TA512,¹⁵ TA542,¹⁶ TA581,¹⁸ TA650,²⁴ and TA645¹⁷), to identify alternative sources of data around costs and utilities that could be used in scenario analyses. Scenario analyses will also be used to explore any structural uncertainties that are identified during validation of the company models or construction of the AG's model.

6.4.6 Presentation of results

Cost effectiveness results will be presented as incremental cost per QALY ratios for each option considered. Results of the deterministic sensitivity analyses will be presented in tornado diagrams. Cost effectiveness acceptability curves will also be presented to demonstrate the uncertainty in the AG's base case cost effectiveness results.

7 Handling the company submissions

When NICE timelines have been finalised, a deadline for receipt of data from the companies/sponsors will be set; data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submissions, provided they comply with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the AG judges that the economic evidence submitted by the companies is not robust, then further work will be undertaken, either by adapting what already exists or developing a de novo model. Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the company checklist, will be highlighted in blue and underlined in the AG's report (followed by an indication of the relevant company name e.g., in brackets). Any 'academic in confidence' data taken from a company submission, and specified as confidential in the company checklist, will be highlighted in yellow and underlined in the AG's report (followed by an indication of the relevant company name e.g., in brackets).

8 Competing interests of authors

This AG comprises the individuals listed in Table 5. Clinical experts will also be consulted during the review process. The experts will provide insight into a range of issues relating to clinical practice, potential patient characteristics that may influence clinical heterogeneity and relevant patient subgroups.

Table 5 Assessment Group members

Nigel Fleeman	Team lead/clinical systematic reviewer	LRiG, University of Liverpool
Rachel Houten	Systematic reviewer (economics) and economic modeller	LRiG, University of Liverpool
James Mahon	Economic modeller	Director, Coldingham Analytical Services, Berwickshire
Sarah Nevitt	Statistician	LRiG, University of Liverpool
Sophie Beale	HTA analyst	Director, Hare Research, North Yorkshire
Angela Boland	HTA analyst	LRiG, University of Liverpool
Janette Greenhalgh	Systematic reviewer (clinical)	LRiG, University of Liverpool
Katherine Edwards	Systematic reviewer (clinical)	LRiG, University of Liverpool
Devarshi Bhattacharyya	Systematic reviewer (economics)	LRiG, University of Liverpool
Michelle Maden	Information specialist	LRiG, University of Liverpool
Rui Duarte	HTA analyst	LRiG, University of Liverpool
Joanne McEntee	Senior Medicines Information Pharmacist	North West Medicines Information Centre, Liverpool
Tom Waddell	Clinical adviser	Consultant in Medical Oncology, Christie NHS Foundation Trust, Manchester
Shien Chow	Clinical adviser	Consultant in Medical Oncology, Clatterbridge Centre NHS Foundation Trust

Tom Waddell has received funds for research from Eisai and Merck Sharp & Dohme (feedback from CLEAR trial²⁶ results, as some of the Christie NHS Foundation Trust patients were enrolled into the trial). Shien Chow has received reimbursement for attending a symposium and fees for speaking from Novartis, EUSA and Pfizer, as well as reimbursement for attending a symposium from ISPEN and funds for a member of staff from Novartis. None of the other members of the review team has any competing interests. Any competing interests relating to any external reviewers will be declared in the final report. All e-mail correspondence should be sent to the TAR team lead (See Section 2).

9 References

1. BMJ Best Practice. Renal Cell Carcinoma. Last updated: Oct 14, 2020. Available from: <https://bestpractice.bmj.com/topics/en-gb/261>. Accessed 10 Sep 2021.
2. Gray RE, Harris GT. Renal Cell Carcinoma: Diagnosis and Management. *Am Fam Physician*. 2019; 99:179-84.
3. Kabaria R, Klaassen Z, Terris MK. Renal cell carcinoma: links and risks. *Int J Nephrol Renovasc Dis*. 2016; 9:45-52.
4. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol*. 2016; 70:93-105.
5. Cancer Research UK. Types and grades. Kidney cancer. Last reviewed: 09 Mar 2020. Available from: <https://www.cancerresearchuk.org/about-cancer/kidney-cancer/stages-types-grades/types-grades>. Accessed 10 Sep 2021.
6. Ahrens M, Scheich S, Hartmann A, Bergmann L. Non-Clear Cell Renal Cell Carcinoma - Pathology and Treatment Options. *Oncology Research and Treatment*. 2019; 42:128-35.
7. Valenca LB, Hirsch MS, Choueiri TK, Harshman LC. Non-clear cell renal cell carcinoma, part 1: histology. *Clin Adv Hematol Oncol*. 2015; 13:308-13.
8. American Cancer Society. Kidney Cancer Stages. Renal Cell Carcinoma Staging. Last Revised: February 1, 2020. Available from: <https://www.cancer.org/cancer/kidney-cancer/detection-diagnosis-staging/staging.html>. Accessed 10 Sep 2021.
9. Cancer Research UK. Kidney cancer incidence statistics. Last reviewed: 5 March 2020. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer/incidence#heading-Zero>. Accessed 10 Sep 2021.
10. Office for National Statistics. Cancer survival in England: adult, stage at diagnosis and childhood - patients followed up to 2018. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/stageatdiagnosisandchildhoodpatientsfollowedupto2018#cancer-survival-by-stage-for-less-common-cancers>. Accessed 10 Sep 2021.
11. Leibovich BC, Blute ML, Cheville JC, Lohse CM, Frank I, Kwon ED, *et al*. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer*. 2003; 97:1663-71.
12. Ljungberg B, Alamdari FI, Rasmuson T, Roos G. Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. *BJU Int*. 1999; 84:405-11.
13. National Institute for Health and Care Excellence (NICE). Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. Technology appraisal guidance [TA169]. Published date: 25 March 2009. Available from: <https://www.nice.org.uk/guidance/ta169>. Accessed 20 Aug 2019.
14. National Institute for Health and Care Excellence (NICE). Pazopanib for the first-line treatment of advanced renal cell carcinoma. Technology appraisal guidance [TA215]. Published date: 23 February 2011. Last updated: 01 August 2013. Available from: <https://www.nice.org.uk/guidance/ta215>. Accessed 20 Aug 2019.
15. National Institute for Health and Care Excellence (NICE). Tivozanib for treating advanced renal cell carcinoma. Technology appraisal guidance [TA512]. Published date: 21 March 2018. Available from: <https://www.nice.org.uk/guidance/ta512>. Accessed 20 Aug 2019.
16. National Institute for Health and Care Excellence (NICE). Cabozantinib for untreated advanced renal cell carcinoma. Technology appraisal guidance [TA542]. Published date: 03 October 2018. Available from: <https://www.nice.org.uk/guidance/ta542>. Accessed 20 Aug 2019.

17. National Institute for Health and Care Excellence (NICE). Avelumab with axitinib for untreated advanced renal cell carcinoma. Technology appraisal guidance [TA645] Published: 02 September 2020. Available from: <https://www.nice.org.uk/guidance/ta645>. Accessed 27 Sep 2021.
18. National Institute for Health and Care Excellence (NICE). Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. Technology appraisal guidance [TA581] Published: 15 May 2019. Available from: <https://www.nice.org.uk/guidance/ta581>. Accessed 23 Sep 2021.
19. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1999; 17:2530-40.
20. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, *et al*. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009; 27:5794-9.
21. Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, *et al*. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *The Lancet Oncology*. 2013; 14:141-8.
22. Kubackova K, Melichar B, Bortlicek Z, Pavlik T, Poprach A, Svoboda M, *et al*. Comparison of Two Prognostic Models in Patients with Metastatic Renal Cancer Treated with Sunitinib: a Retrospective, Registry-Based Study. *Targeted oncology*. 2015; 10:557-63.
23. National Institute for Health and Care Excellence (NICE). Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. Technology appraisal guidance [TA178]. Published: 26 August 2009. Available from: <https://www.nice.org.uk/guidance/ta178>. Accessed 24 Sep 2021.
24. National Institute for Health and Care Excellence (NICE). Pembrolizumab with axitinib for untreated advanced renal cell carcinoma. Technology appraisal guidance [TA650]. Published: 30 September 2020. Available from: <https://www.nice.org.uk/guidance/ta650>. Accessed 24 Sep 2021.
25. US Food & Drug Administration (FDA). FDA approves lenvatinib plus pembrolizumab for advanced renal cell carcinoma. Available from: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-plus-pembrolizumab-advanced-renal-cell-carcinoma>. Accessed 27 Sep 2021.
26. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, *et al*. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med*. 2021; 384:1289-300.
27. National Institute for Health and Care Excellence (NICE). Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [CDF Review of TA581]. In progress. Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-ta10854>. Accessed 6 Oct 2021.
28. National Institute for Health and Care Excellence (NICE). Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. January 2019. Available from: <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf>. Accessed 8 Oct 2021.
29. National Institute for Health and Care Excellence (NICE). Lenvatinib with everolimus or pembrolizumab for untreated advanced renal cell carcinoma [ID3760]. In development [GID-TA10629]. Expected publication date: 19 January 2023. Available

- from: <https://www.nice.org.uk/guidance/indevelopment/gid-ta10629>. Accessed 24 Sep 2021.
30. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. CRD, University of York. 2009; Available from: <https://www.york.ac.uk/crd/guidance/>. Accessed 20 Sep 2021.
 31. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009; 6:e1000097.
 32. European network for Health Technology Assessment (EUnetHTA). Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness. Version 2.0, December 2019. Available from: https://www.eunetha.eu/wp-content/uploads/2020/01/EUnetHTA_Guideline_Information_Retrieval_v2-0.pdf. Accessed 21 Sep 2021.
 33. National Institute for Health Research (NIHR). PROSPERO: International database of prospectively registered systematic reviews in health and social care Available from: <https://www.crd.york.ac.uk/prospéro/>. Accessed 20 Sep 2021.
 34. The EndNote Team. EndNote X9. Philadelphia, PA: Clarivate; 2013.
 35. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available from: www.covidence.org. Accessed 24 Sep 2021.
 36. Phillippo DM. multinma: Network meta-analysis of individual and aggregate data in Stan. doi: 10.5281/zenodo.3904454. R package version 0.3.0. 2021; Available from: <https://dmphillippo.github.io/multinma/>. Accessed 23 Sep 2021.
 37. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. *Statistics and Computing*. 2000; 10:325-37.
 38. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011. Available from: <http://nicedsu.org.uk/technical-support-documents/evidence-synthesis-tsd-series/>. Accessed 23 Sep 2021.
 39. Dias S, Sutton AJ, Welton NJ, Ades A. NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. 2011; last updated April 2012. Available from: <http://nicedsu.org.uk/technical-support-documents/evidence-synthesis-tsd-series/>. Accessed 23 Sep 2021.
 40. Dias S, Welton NJ, Sutton AJ, Caldwell D, Lu G, Ades AE. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011; last updated April 2014. Available from: <http://nicedsu.org.uk/technical-support-documents/evidence-synthesis-tsd-series/>. Accessed 23 Sep 2021.
 41. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81:515-26.
 42. Freeman SC, Carpenter JR. Bayesian one-step IPD network meta-analysis of time-to-event data using Royston-Parmar models. *Res Synth Methods*. 2017; 8:451-64.
 43. Wiksten A, Hawkins N, Piepho H-P, Gsteiger S. Nonproportional Hazards in Network Meta-Analysis: Efficient Strategies for Model Building and Analysis. *Value in Health*. 2020; 23:918-27.
 44. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al*. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ : British Medical Journal*. 2013; 346:f1049.
 45. National Institute for Health and Care Excellence (NICE). Guide to the Methods of Technology Appraisal. 2013; Available from: <https://www.nice.org.uk/process/pmg9/chapter/foreword> Accessed 22 Aug 2021.
 46. British National Formulary. BNF. 2021; Available from: <http://www.bnf.org/bnf/>. Accessed 11 Oct 2021.

47. Department of Health and Social Care. NHS Electronic Marketing Information Tool [eMIT] 2021; Available from: <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>. Accessed 11 Oct 2021.
48. Curtis LA, Burns A. Unit Costs of Health and Social Care 2020. Available from: <https://www.pssru.ac.uk/project-pages/unit-costs/>. Accessed 22 Aug 2021.
49. National Health Service (NHS). National schedule of reference costs 2019/20. 2018; Available from: <https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/>. Accessed 22 Aug 2021.

10 Appendices

10.1 Appendix 1: Search strategies

Table 6 Summary of approaches to searching for evidence

	Clinical effectiveness	Cost effectiveness
Databases	MEDLINE EMBASE PubMed Cochrane Library (CENTRAL) INAHTA	MEDLINE EMBASE PubMed Cochrane Library (CENTRAL) INAHTA NHS EED EconLit CEA Registry
Limits	English language	English language From 2006 onwards
Search terms	Disease area (free text and keywords) RCT filter (see example MEDLINE search, Section 10.1.1)	Disease area (free text and keywords) Economics filter (see example MEDLINE search, Section 10.1.2)
Other sources	Conference websites: <ul style="list-style-type: none"> • ASCO • ASGO-GU • ESMO • ECCO • HTAi <p>Trial registries:</p> <ul style="list-style-type: none"> • Clinical trials.gov • ICTRP • EU-CTR <p>Company submissions to NICE in current and previous related appraisals (TA169,¹³ TA178,²³ TA215,¹⁴ TA512,¹⁵ TA542,¹⁶ TA581,¹⁸ TA650,²⁴ and TA645¹⁷)</p> <p>Regulatory reports (e.g., SMC, CADTH, HAS, PBAC, EMA, MHRA and FDA)</p> <p>Contacting clinical experts</p>	Conference websites: <ul style="list-style-type: none"> • ASCO • ASGO-GU • ESMO • ECCO • HTAi • ISPOR <p>Company submissions to NICE in current and previous related appraisals (TA169,¹³ TA178,²³ TA215,¹⁴ TA512,¹⁵ TA542,¹⁶ TA581,¹⁸ TA650,²⁴ and TA645¹⁷)</p> <p>Regulatory reports (e.g., SMC, CADTH, HAS, PBAC, EMA, MHRA and FDA)</p>

ASCO=American Society of Clinical Oncology; ASGO-GU=American Society of Clinical Oncology Genitourinary; CADTH=Canadian Agency for Drugs and Technologies in Health; CEA=Cost Effectiveness Analysis; ECCO=European Conference for Clinical Oncology; EMA=European Medicines Agency; ESMO=European Society for Medical Oncology; EU-CTR=European Union Clinical Trials Register; FDA=US Food and Drug Administration; HAS=Haute Autorité de Santé; HTAi=Health Technology Assessment International; ICTRP=International Clinical Trials Registry Platform; INAHTA= International Health Technology Assessment; ISPOR=International Society for Pharmacoeconomics and Outcomes Research; MHRA=Medicines and Healthcare products Regulatory Agency; PBAC=Pharmaceutical Benefits Advisory Committee; RCT=Randomised controlled trial; SMC=Scottish Medicines Consortium; TA=technology appraisal

10.1.1 Example search strategy (MEDLINE): clinical effectiveness

1 exp Carcinoma, Renal Cell/ 35734
2 exp Kidney Neoplasms/ 78119
3 (renal adj2 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw. 60510
4 (kidney adj1 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw. 9171
5 (clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw. 51
6 (non?clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw. 1
7 hypernephroma.tw,kw. 1263
8 hypernephroid carcinoma*.tw,kw. 82
9 grawitz tumo?r\$.tw,kw. 117
10 rcc.tw,kw. 16816
11 or/1-10 100673
12 (advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable).tw,kw. or Neoplasm Metastasis/ 1364344
13 11 and 12 33711
14 (mrcc or arcc).tw,kw. 2285
15 13 or 14 33902
16 randomized controlled trial.pt. 544498
17 controlled clinical trial.pt. 94426
18 (randomized or randomised).ab. 639708
19 placebo.ab. 221714
20 clinical trials as topic.sh. 197498
21 randomly.ab. 366508
22 trial.ti. 248175
23 (randomised or randomized or RCT).m_titl. 230834
24 or/16-23 1445463
25 exp animals/ not humans.sh. 4890266
26 24 not 25 1332768
27 15 and 26 2718
28 limit 27 to English language 2562

10.1.2 Example search strategy (MEDLINE): cost effectiveness

1 exp Carcinoma, Renal Cell/ 35734
2 exp Kidney Neoplasms/ 78119
3 (renal adj2 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw. 60510
4 (kidney adj1 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw. 9171
5 (clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw. 51
6 (non?clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw. 1
7 hypernephroma.tw,kw. 1263
8 hypernephroid carcinoma*.tw,kw. 82
9 grawitz tumo?r\$.tw,kw. 117
10 rcc.tw,kw. 16816
11 or/1-10 100673
12 (advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable).tw,kw. or Neoplasm Metastasis/ 1364344
13 11 and 12 33711
14 (mrcc or arcc).tw,kw. 2285
15 13 or 14 33902
16 Economics/ 27375
17 exp "Costs and Cost Analysis"/ 249515
18 Economics, Nursing/ 4007
19 Economics, Medical/ 9156
20 Economics, Pharmaceutical/ 3022
21 exp Economics, Hospital/ 25308
22 Economics, Dental/ 1919
23 exp "Fees and Charges"/ 30886
24 exp Budgets/ 13891
25 budget*.ti,ab,kf. 32169
26 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. 249156
27 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. 953323
28 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 180632
29 (value adj2 (money or monetary)).ti,ab,kf. 2656
30 exp models, economic/ 15816
31 economic model*.ab,kf. 3660
32 markov chains/ 15265
33 markov.ti,ab,kf. 25050
34 monte carlo method/ 30182
35 monte carlo.ti,ab,kf. 53530
36 exp Decision Theory/ 12600
37 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. 28529
38 or/16-37 1285749
39 15 and 38 580
40 limit 39 to English language 538

10.2 Appendix 2: Draft data extraction forms

10.2.1 Examples clinical effectiveness data to be extracted

Study details

- Endnote reference (in the form of xyz, no '#')
- Author (e.g., Jones et al.)
- Year (i.e., year of publication or date of interim data collection)
- Study design (summary of study design and details of subgroup analyses [if any])
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Follow-up duration

Intervention details

Data for each intervention will be entered in the following format:

- Intervention (i.e., drug name[s])
- Dose(s) of intervention(s) (dose)

Participant characteristics

Data for each intervention will be entered in the following format:

- Number of participants enrolled
- Number of participants lost to follow up
- Demographic information (age, sex/gender, region, race/ethnicity)
- Disease characteristics (performance status, risk status, PD-L1 status, histology, time since diagnosis, prior nephrectomy, number of metastatic sites, sites of metastatic disease)

Outcomes: definitions and measures

- Description of outcomes reported:
 - Outcomes reported that are relevant to the decision problem (including description of how defined)
 - Other outcomes reported in the trial not relevant to the decision problem
- Results of Outcomes reported that are relevant to the decision problem

10.2.2 Examples cost effectiveness data to be extracted

Study details

- Endnote reference (in the form of xyz, no '#')
- Author (e.g., Jones et al.)
- Year (i.e., year of publication or date of interim data collection)
- Type of economic evaluation (cost effectiveness analysis, cost utility analysis, cost minimisation analysis and cost benefit analysis)

Intervention and comparator details

Data for each intervention will be entered in the following format:

- Intervention and comparator (i.e., drug name[s])

Model overview

- Model structure (i.e., Markov, partitioned survival)
- Health states
- Time horizon
- Cycle length
- Discount rates for costs and benefits
- Perspective used (country, healthcare system, societal)
- Sources of clinical evidence
- Sources of utilities evidence [if using QALYs as an outcome]
- Sources of costs evidence
- Currency used
- Year to which costs apply

Outcomes

- Total costs
- Total QALYs
- Total LYs
- Incremental costs
- Incremental QALYs
- Incremental LYs
- ICER per LY gained
- ICER per QALY gained
- Sensitivity analysis results
- Authors conclusions of cost effectiveness results and limitations