NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment

Submitted by Pfizer Ltd.

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

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Abbreviations

AE	Adverse event
BD	Twice daily
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
c-KIT	Stem cell factor receptor
CR	Complete response
CrI	Credible interval
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of life questionnaire version 3.0
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
FKSI	Functional Assessment of Cancer Therapy Kidney Symptom Index
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index -Disease Related Symptoms
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IC	Indirect comparison
IFN-α	Interferon-alpha
IL-2	Interleukin-2
IRC	Independent review committee
ITT	Intent-to-treat
Mg	Milligrams
mRCC	Metastatic renal cell carcinoma
MSKCC	Memorial Sloan-Kettering Cancer Centre
mTOR	Mammalian target of rapamycin
NICE	National Institute for Health and Clinical Excellence
NR	Not reported
OR	Objective response
ORR	Objective response rate

OS	Overall survival
PD	Progressive disease
PDGF	Platelet-derived growth factor
PDGFR-β	Platelet-derived growth factor receptor beta
PenTAG	Peninsula Technology Assessment Group
PF	Progression free
PFS	Progression-free survival
PR	Partial response
PS	Performance status
PSS	Personal Social Services
QD	Once daily
QOD	Every other day
QoL	Quality of life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RENCOMP	Renal Comparison
RPSFT	Rank preserving structural failure time
SAE	Serious adverse event
SAS	Safety analysis set
SMC	Scottish Medicines Consortium
STC	Simulated treatment comparison
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TTD	Time to deterioration
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VEGFR-TKI	Vascular endothelial growth factor receptor tyrosine kinase inhibitor
VHL	Von Hippel-Lindau

Executive summary

Renal cell carcinoma (RCC) is the collective name for a group of cancers that originate in the kidney within the epithelia of the renal tubules. Kidney cancer is a rare cancer and accounts for 3% of male cancers and 2% of female cancers in the UK. There are approximately 8163 incident kidney cancers in England and Wales every year and RCC accounts for 90% of all kidney cancers. Of these patients, 27% and 14% are expected to have stage III and IV (advanced/metastatic (m)RCC) disease, respectively, and 33% of former stage I-II are expected to recur to stage III-IV, resulting in approximately 4456 patients diagnosed with advanced/mRCC per year (NICE TA169). It is estimated that approximately 1580 patients each year would be eligible for second line treatment with axitinib.

Advanced/mRCC places a considerable burden on society and patients. The symptoms of metastatic disease, and the generally poor prognosis contribute to the substantial negative impact of advanced/mRCC on survival and aspects of HRQoL, such as physical functioning, energy and fatigue level, mental status, sexual functioning, and perceived well-being.

Surgical excision is the only curative treatment option for localised RCC. There is no cure for advanced/mRCC, therefore the goals of medical intervention are to extend life, prevent worsening of disease, relieve symptoms and maintain physical function. Advanced/mRCC is largely unresponsive to chemotherapy, radiotherapy and hormonal therapy. Prior to targeted therapies, systemic treatment of advanced/mRCC primarily included the cytokines interleukin-2 (IL-2) and IFN-α; however these treatments are associated with limited efficacy and high toxicity, with only a small minority of patients achieving a durable response with high dose IL-2. Treatment with cytokines accounts for approximately 5% of all first-line advanced/mRCC patients in the UK.

In recent years there has been a paradigm shift in the management of advanced/mRCC with the development of targeted therapies. These therapies have focused on two pathways that are commonly de-regulated in RCC, the vascular endothelial growth factor receptor (VEGFR) pathway which is targeted by tyrosine kinase inhibitors (TKIs) such as sunitinib and pazopanib, and the mammalian target of rapamycin (mTOR) pathway which is targeted by mTOR inhibitors such as temsirolimus and everolimus.

The existing NICE guidance recommends the VEGFR-TKIs, sunitinib and pazopanib, for the first-line treatment of advanced/mRCC. Treatment with these therapies accounts for approximately 95% of all first-line advanced/mRCC patients in the UK. Despite the clear clinical benefits observed with first-line therapies in terms of improved progression free and overall survival, resistance occurs. The majority of patients initially respond to therapy but go on to experience disease progression. NICE does not currently recommend any interventional therapies for advanced/mRCC following failure of initial first-line systemic therapy and on this basis patients would receive best supportive care (BSC), the relevant comparator in this appraisal. While everolimus and sorafenib are licensed in the UK, neither are recommended by NICE. Everolimus is commonly funded through the Cancer Drugs Fund in second and third line, while sorafenib is not widely used in UK clinical practice.

Prior to the introduction of targeted therapy, patients who have been treated with cytokines or other agents lived a median of 10 to 13 months from the start of treatment. Prognosis is poor when patients that have become refractory to first-line therapy are left untreated. It is reported that UK patients survived approximately 4 months (median) on BSC once they have progressed following treatment with sunitinib. In addition, these patients are expected to rapidly progress and experience a significant deterioration in their HRQoL.

As advanced/mRCC patients who become refractory to first-line therapy have no effective treatment options, there is a clear unmet need for a therapy that maintains quality of life and extends progression-free and overall survival (OS).

Axitinib (Inlyta®) is a next-generation, oral VEGFR-TKI. Axitinib selectively inhibits the VEGFR receptors (VEGFR)-1, -2, and -3 with greater potency and selectivity than currently available VEGFR-TKIs.

Axitinib received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 24th May 2012, recommending a marketing authorisation for the treatment of adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine.

Axitinib is the first VEGFR-TKI proven to be superior over an active comparator, sorafenib, in a large purely second-line population in a randomised phase III open label trial (AXIS). Although the study was powered to investigate the progression free survival (PFS) for the ITT patient population and not subgroups, axitinib superiority was observed in ITT population in addition to both the sunitinib refractory (55% n=389) and the cytokine refractory subgroups (35% n=251). These subgroups account for about 90% of the ITT trial population.

In line with the CHMP opinion, results are presented in separate analyses within the submission for the sunitinib and cytokine refractory subgroups. Separate analyses were neccessary as cytokine refractory patients, whom are TKI naïve, are considered by clinicians to comprise a markedly different subgroup of patients compared with those who are sunitinib refractory. The cytokine refractory patients may have failed more rapidly than a population exposed to TKIs in the first-line setting and therefore may be an easier population to treat with a TKI in a second-line setting. The marked differences between these two populations are reflected by the differences in PFS, OS and tumour response achieved by the cytokine refractory and the sunitinib refractory population in the AXIS study.

Axitinib demonstrated significant improvements in PFS compared with sorafenib for patients who had failed first-line sunitinib or cytokine therapy. In the sunitinib-refractory subgroup, median PFS in the axitinib arm was 4.8 months compared with 3.4 months in patients treated with sorafenib (HR 0.741; 95% CI, 0.573 to 0.958; p=0.0107). In the cytokine-refractory subgroup, median PFS was 12.1 months in the axitinib arm compared with 6.5 months in the sorafenib arm (HR 0.464; 95% CI, 0.318 to 0.676; p<0.0001).

Median OS in the axitinib arm and sorafenib arm for the sunitinib-refractory subgroup was 15.2 months and 16.5 months respectively. Median OS in in the axitinib arm and sorafenib arm for the cytokine refractory subgroup was 29.4 months and 27.8 months respectively. There was no significant difference between axitinib and sorafenib for

median OS in the sunitinib-refractory subgroup (HR 0.997; 95% CI, 0.782 to 1.270; p=0.4902) or the cytokine-refractory subgroup (HR 0.813; 95% CI, 0.555 to 1.191; p=0.1435). Possible reasons for the lack of apparent OS benefit with axitinib vs sorafenib despite the clear PFS benefit include the limitations of active comparator studies, the difficulty of demonstrating incremental OS benefit in advanced/mRCC, confounding due to long duration of survival post-progression and confounding due to post-study treatment.

Axitinib allows patients to maintain their HRQoL for longer by providing a greater PFS benefit than sorafenib. HRQoL as measured by Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI), FKSI-disease related symptoms (FKSI-DRS) and EuroQol-5D (EQ-5D) was maintained with both therapies while patients were on treatment, but declined when patients stopped study medication (mainly due to progression).

Adverse events (AEs) reported for patients treated with axitinib in the pivotal Phase III trial were generally mild or moderate in severity and clinically manageable. The AE profile was consistent with the mechanism of action of axitinib. The most common treatment-emergent AEs experienced in the axitinib arm were diarrhoea (54.9%), hypertension (40.4%) and fatigue (39.0%), most of which were mild or moderate in severity.

The axitinib pivotal trial (AXIS) was performed against sorafenib; thus no head-to-head data are available for axitinib vs BSC for the sunitinib and cytokine refractory subgroups. A systematic review of RCT evidence for the second-line treatment of advanced/mRCC was carried out to identify appropriate studies to include in an indirect comparison of axitinib vs BSC. Considering the evidence network for the two subgroups separately, the results of the review showed that an indirect comparison between axitinib and BSC was only possible in the cytokine refractory subgroup using the AXIS trial and the TARGET trial (pivotal phase III trial for sorafenib versus placebo (used as a proxy for BSC). The TARGET trial was appropriate for this population as it was performed in a population that was predominantly cytokine refractory. For the sunitinib refractory population, it was not feasible to perform an indirect comparison due to the lack of available RCT evidence comparing sorafenib and BSC in this population. To address the lack of direct and indirect comparative evidence of axitinib versus BSC in a sunitinib refractory population, a simulated treatment comparison (STC) was performed. This is a statistical method that simulates the “missing arms” of a randomised trial. The analyses carried out for these separate populations are summarised below.

In the cytokine-refractory population the indirect comparison resulted in an estimated PFS hazard ratio for axitinib vs placebo in a cytokine-refractory population of 0.251 (95% Credible interval (CrI) 0.165-0.379), indicating that axitinib reduced the risk of progression by 75% compared with a placebo treated patient. For the OS endpoint when the comparison was performed using the population that were censored for cross-over in the TARGET trial, the hazard ratio was 0.63 (CrI 0.41-0.99), indicating a 37% reduction in the risk of death compared with a placebo treated patient. However, a considerable limitation to the indirect comparison for OS was the bias due to substantial crossover from placebo to sorafenib in the TARGET study. This resulted in an underestimation of the incremental OS benefit of sorafenib versus BSC in the TARGET trial and consequently an undestimation of the OS benefit of axitinib versus BSC in the indirect

comparison. While an analysis censoring patients for cross-over in the TARGET trial was available and used in the indirect comparison, a more appropriate method of adjusting for cross-over such as Rank-Preserving Structural Failure Time (RPSFT) was not available to reduce the uncertainty introduced by this bias.

As mentioned above, for the sunitinib refractory population, it was not appropriate to indirectly compare axitinib and BSC using the AXIS and TARGET trials. The TARGET trial does not have a sunitinib refractory population and as previously discussed the cytokine and sunitinib refractory populations are clinically distinct as indicated by the higher median PFS, median OS and tumour response achieved by the cytokine refractory population in the AXIS study versus the sunitinib refractory population. Combining the two populations would generate considerable heterogeneity in the results of any analysis due to the clinical differences between the populations. Furthermore the cross-over in the TARGET study would introduce additional bias as mentioned above.

An STC was conducted to create an "adjusted" comparison between the axitinib sunitinib-refractory population from AXIS and the BSC ITT population from RECORD-1. The RECORD-1 trial (the pivotal Phase III trial of everolimus v BSC in a prior TKI population) was the only study apart from AXIS identified by the systematic review that reported data on patients that received BSC following sunitinib treatment and was therefore used in the STC analysis. The STC used predictive equations for key endpoints (PFS and OS) derived from the index trial (AXIS), which were adjusted to match the prognostic patient characteristics of RECORD-1, allowing for an adjusted side-by-side comparison of the two trial populations. Similar approaches have been accepted in recent HTA decisions. This method produced an estimated median PFS of 1.7 months for axitinib-like patients if they had received placebo compared to 6.3 months for axitinib. The estimated median OS was 8.3 months for axitinib-like patients assuming that they received placebo compared to 16.6 months for axitinib. Overall, in the sunitinib-refractory population axitinib improved median PFS by 4.6 months and median OS by 8.3 months compared to placebo.

First-line and second-line therapies for the treatment of advanced/mRCC are considered to be end of life treatments and it is anticipated that axitinib will also fulfill the requirements to be considered an end of life treatment. Evidence from the comparative efficacy data analyses outlined above demonstrate that axitinib prolongs survival by at least 3 months versus BSC in a small patient population (less than 7,000) whose life expectancy is likely to be substantially less than 24 months if not treated in the second line setting.

An economic model was developed to assess the cost-effectiveness of axitinib compared with BSC in patients with advanced/mRCC after failure of prior treatment with sunitinib or a cytokine. The model was aligned with those used in previous NICE appraisals in advanced/mRCC. In both sunitinib refractory and cytokine refractory populations, axitinib was associated with higher costs but provided additional quality adjusted life years (QALYs) vs BSC. The base case incremental cost per QALY gained versus BSC in the cytokine and sunitinib refractory subgroups were [redacted] and [redacted] respectively.

One-way sensitivity analyses, scenario analyses and probabilistic sensitivity analyses showed that the findings were relatively robust to changes in key parameters. The key source of uncertainty in the model is the absolute survival estimate produced by the

model for treatment with BSC. However, model results can be viewed as a conservative estimation of second-line advanced/mRCC patients receiving BSC based on estimates used in previous appraisals and published literature.

The base case incremental cost-effectiveness ratio (ICER) for sunitinib refractory patients who represent the vast majority of second-line advanced/mRCC patients in the UK is close to the accepted thresholds for other end of life treatments. For cytokine refractory patients, the base case ICER is higher than the accepted thresholds for other end of life treatments but as mentioned previously the ICER is an over-estimation in this population due to the limitations of the evidence network such as the bias introduced in the OS analysis by the cross-over in the TARGET study.

The budget impact of introducing axitinib for patients with advanced/mRCC refractory to sunitinib and cytokines in England and Wales has been estimated to be [redacted] annually over a period of 5 years. [redacted]

In conclusion,axitinib should be a recommended treatment option in the NHS for the following reasons:

- This document provides evidence that axitinib is expected to fulfil end of life criteria, specifically:
    - Patients with advanced/mRCC have a very poor prognosis if untreated after progression on first line therapy, and are expected to survive less than 24 months and as low as 4 months in a sunitinib-refractory population
    - Axitinib is expected to offer more than 3 months additional survival over BSC in the post-cytokine and post-sunitinib populations
    - Advanced/mRCC patients who have received prior treatment with cytokines or sunitinib constitute a small patient population.
- Axitinib efficacy and tolerability has been demonstrated in a patient population refractory to the most widely used first line targeted therapy, sunitinib, and therefore, representative of UK clinical practice. Axitinib has the potential to fulfil a substantial unmet need in the treatment of a severe end-of-life disease, with negative burden on society and patients and where no other second line treatments have currently been recommended by NICE. As such axitinib is anticipated to lead to a step change in the second-line management of advanced/mRCC after treatment failure with sunitinib or a cytokine.
- Therefore the recommendation of axitinib by NICE would be a cost-effective use of NHS resources in a small population with limited budget impact fulfilling the end of life criteria.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Generic name: Axitinib

Brand name: Inlyta®

Approved name: Inlyta® 1mg and 5mg film-coated tablets

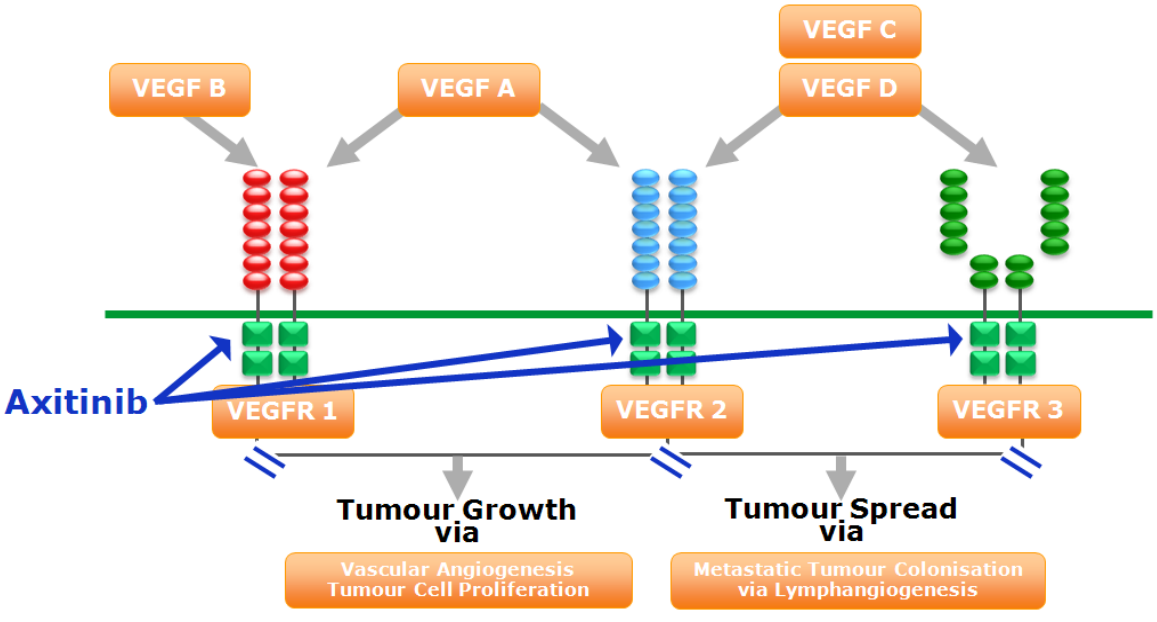
Therapeutic class: Axitinib is an antineoplastic agent, belonging to the protein kinase inhibitor class of drugs. The Anatomical Therapeutic Chemical (ATC) Classification Code is L01XE17.

1.2 What is the principal mechanism of action of the technology?

Axitinib is the first, next-generation, oral vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI). Axitinib selectively inhibits the VEGF receptors (VEGFR)-1, -2, and -3 with greater potency and selectivity than currently available VEGFR-TKIs. Clinical data from the Phase III trial where axitinib demonstrated superiority in progression-free survival (PFS) over sorafenib support the hypothesis that more potent biochemical targeting of the VEGFRs is associated with superior clinical activity in advanced/metastatic renal cell carcinoma (mRCC). VEGF is a crucial mediator of angiogenesis, the process whereby tumours gain the ability to develop rich blood supplies, allowing them to grow and metastasise. VEGFR-1 regulates the proliferation of endothelial cells (1) and promotes cell migration and invasion (2). VEGFR-2 promotes growth, migration, and tubular formation of endothelial cells and enhances vascular permeability (3-5). VEGFR-3 promotes the development of lymphatic vessels (lymphangiogenesis) (6).

A schematic of the role of VEGFR-1, -2 and -3 and the point of action of axitinib is presented in Figure 1.

Figure 1: Role of VEGF signalling in tumour progression and the point of action of axitinib



Axitinib has little or no activity against colony-stimulating factor (CSF)-1R, fms-like tyrosine kinase (FLT)-3, fibroblast growth factor receptor (FGF)-1R, ret proto-oncogene (RET), epidermal growth factor receptor (EGFR), and met proto-oncogene encoding hepatocyte growth factor (c-Met) (7). Therefore, differences in the receptor selectivity/potency profiles may explain the different adverse event profiles of currently available VEGFR-TKI inhibitors observed in clinical practice.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On 24th May 2012, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion, recommending the granting of a marketing authorisation for axitinib for the treatment of adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine. The CHMP considered there to be a favourable benefit-to-risk balance for axitinib on the basis of quality, safety and efficacy data submitted and recommended the granting of the marketing authorisation. Marketing authorisation from the European Commission is expected in September or October 2012.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The main issues encountered during the regulatory review process focused on the subgroup populations of the pivotal Phase III Study A4061032. The CHMP consulted the

Scientific Advisory Group on Oncology about the choice of comparator, the place of axitinib in second-line advanced/mRCC and the benefit-risk profile of axitinib according to prior treatment. In the Phase III trial, eligible prior first-line treatments included all those licensed at the time of the trial design. Pazopanib a first-line treatment option currently available to UK patients was not licensed at the time of the phase III trial design. Patients could have had one of four prior treatments, sunitinib (54% n=389), a cytokine (35% n=251), bevacuzimab + interferon alpha (IFN-α) (8% n=59) or prior temsirolimus (3% n=24). In June 2011, Pfizer filed for regulatory review of axitinib for the treatment of patients with advanced RCC after failure of systemic treatment with the European Medicines Agency (EMA) which is reflected in the final scope of this appraisal. The EMA CHMP positive opinion to recommend use of axitinib after failure of sunitinib or a cytokine is based on subsequent analysis of Phase III data from the AXIS trial that supports Pfizer's submission. Therefore for the purpose of this appraisal, the sunitinib refractory and cytokine refractory subgroups will be the focus of this single technology appraisal in line with the CHMP positive opinion. The clinical data in the temsirolimus refractory and bevacizumab + IFN-α refractory subgroups were considered insufficient to draw any firm conclusions and were thus not included in the proposed licensed indication.

As follow-up requirements to the proposed licence, Pfizer are committed to a molecular profiling program where biomarkers are analysed with regard to potential association to axitinib efficacy.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The anticipated indication for axitinib, based on the positive opinion adopted by the CHMP, is "for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine".

In this context, advanced RCC is defined as patients who have locally advanced or metastatic disease in keeping with the patient population in the CHMP opinion.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The following studies to assess the efficacy and safety of axitinib are ongoing. This list focuses on studies in the second-line treatment of advanced/mRCC.

- Study A4061051 (NCT00920816) is a Phase III, randomised, open-label, international trial designed to compare the efficacy and safety of axitinib vs sorafenib in the first-line or second-line or greater treatment of mRCC (8). This study has completed enrolment of 200 patients from Asia (China, Philippines, Malaysia and Taiwan) who have received previous treatment for mRCC. The primary endpoint in this study is progression-free survival (PFS). Secondary endpoints include overall survival (OS), response rate, duration of response and safety. Final data collection for the primary outcome measure took place in June 2012 and data are expected in Q1 2013.
- Study A4061061 (NCT01473043) is a Phase III/IV, single-arm, multicentre study based in Canada and Australia to investigate the efficacy and safety of axitinib in

patients with mRCC who failed first-line therapy (9). The estimated study completion date is December 2012.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated date of commercial availability in the UK is October 2012.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Axitinib received Food and Drug Administration (FDA) approval in the US on 27th January 2012 for "the treatment of advanced RCC after failure of one prior systemic therapy". Swiss Medic approved axitinib "for the treatment of patients with advanced RCC after failure of a prior systemic treatment" in April 2012. Health Canada approved axitinib "for the treatment of patients with metastatic renal cell carcinoma (RCC) of clear cell histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI, sunitinib" in July 2012 (10). Pfizer have applied for European marketing authorisation through the EMA centralised procedure for axitinib and the product is expected to be licensed throughout Europe.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Pfizer Ltd plan to submit an application to the Scottish Medicines Consortium in Q3 2012.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1: Unit costs of technology being appraised

Pharmaceutical formulation	1 mg film-coated tablets. 5 mg film-coated tablets.
Acquisition cost (excluding VAT)	NHS list price is £3,517 (5mg/56 tablets), £703.40 (1mg/56 tablets)
Method of administration	Oral
Doses	5 mg twice daily (recommended starting dose) Range: 2–10mg twice daily
Dosing frequency	Twice daily continuous dosing
Average length of a course of treatment	Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs that can't be managed by concomitant medicinal products or dose adjustments
Average cost of a course of treatment	Median cost per patient: £18,329 per sunitinib refractory patient £46,203 per cytokine refractory patient. Based on NHS list price, 5mg twice daily dose and a median treatment duration of 4.8 and 12.1 months respectively

Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Recommended starting dose is 5 mg BD. Dose adjustment is not required on the basis of age, race, gender, or body weight. Dose titration allows flexibility in achieving the most appropriate dose for the patients. Dose increase or reduction is recommended based on individual safety and tolerability.Overall in the AXIS study, the percentage of patients dose titrating up and down were similar with the average dose being 10 mg daily with a relative dose intensity of 102% Dose increase or reduction is recommended based on individual safety and tolerability. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy. When dose reduction is necessary, the axitinib dose may be reduced to 3 mg BD and further to 2 mg BD. Patients who tolerate the starting dose of 5 mg BD with no adverse reactions >Grade 2 (CTCAE) for 2 consecutive weeks may have their dose increased to 7 mg BD unless the patient's blood pressure is >150/90 mm Hg or the patient is receiving antihypertensive treatment. Subsequently, using the same criteria, patients who tolerate a dose of 7 mg BD may have their dose increased to a maximum of 10 mg BD.

Abbreviations: BD, twice daily; CTCAE, common terminology criteria for adverse events; mg, milligrams; mm Hg, millimetres of mercury; RCT, randomised controlled trial; RDI, relative dose intensity; VAT, value added tax.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

There are no additional tests or investigations needed for selection of patients for axitinib treatment. Axitinib treatment should be initiated by a physician experienced in the use of anti-cancer therapies. Axitinib tablets should be taken orally, twice-daily, approximately 12 hours apart, with or without food. The tablets should be swallowed whole with a glass of water.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Consultant monitoring and blood tests are expected to be similar to the schedule for best supportive care (BSC). Patients treated with axitinib should be monitored at baseline and periodically for hypertension, thyroid function, and proteinuria. Patients should be treated as necessary according to standard medical practice.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

There are no specific therapies that need to be administered alongside axitinib. Patients may require concomitant medications to manage the symptoms of advanced/mRCC – this is considered standard practice and not specific to patients receiving axitinib treatment.

2 Context

Key points:

- Renal cell carcinomas (RCC) are highly vascularised tumours that originate within the epithelia of the renal tubules and are rare cancers, accounting for 3% of male cancers and 2% of female cancers in the UK. Up to one third of patients present with metastatic disease at the time of diagnosis.
- NICE does not currently recommend any interventional therapies for advanced/mRCC following failure of initial systemic therapy.
- There is a clear unmet need for an effective second-line therapy for the treatment of patients with advanced/mRCC who have become refractory to first-line therapy, in order to maintain quality of life and extend progression-free and overall survival.
    - There is no cure for advanced/mRCC, therefore the goals of medical intervention are to extend life, prevent worsening of disease, relieve symptoms and maintain physical function.
    - Advanced/mRCC is largely unresponsive to chemotherapy, hormonal therapy and radiotherapy.
    - The prognosis of patients with advanced/mRCC is poor, with a 5-year survival of approximately 10%.
    - Two studies of UK patients reported that median survival following treatment with sunitinib was approximately 4 months after disease progression.
    - Health Related Quality of Life (HRQoL) is negatively impacted in patients with advanced/mRCC and deteriorates when patients experience disease progression.
    - The sequential use of VEGFR-TKI therapy for patients following progression on first-line VEGFR-TKI treatment is supported by a growing body of evidence from real-world retrospective analyses and Phase II studies.
- Axitinib is the first, next-generation, oral, vascular endothelial growth factor receptor (VEGFR)-TKI. It selectively inhibits the VEGF receptors 1, 2, and 3 with greater potency and selectivity than currently available VEGFR-TKIs. Clinical data from the Phase III trial where axitinib demonstrated superiority in PFS over sorafenib support the hypothesis that more potent biochemical targeting of the VEGFRs is associated with superior clinical activity in advanced/mRCC. Axitinib is the first and only VEGFR-TKI proven to be superior over an active comparator in a purely second-line patient population. Efficacy results in the sunitinib refractory population in the AXIS trial further validates the clinical benefits of TKI to TKI sequencing in advanced/mRCC.
- The AXIS trial population is highly relevant to the UK. In the trial, 55% of patients (n=389) were reflective of current UK standard-of-care, having received a single previous first-line treatment with sunitinib.
- Axitinib is generally well tolerated, with manageable adverse events.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Renal cell carcinoma

Renal cell carcinoma (RCC) is the collective name for a group of cancers that originate within the epithelia of the renal tubules. RCC accounts for 90% of all kidney cancers diagnosed in England and Wales (11) and 80–90% of these are of the clear cell histological subtype (12). Other less common subtypes include papillary and chromophobe RCC.

Prevalence and incidence in the UK/ England and Wales

In the UK, kidney cancer accounts for 3% of male cancers and 2% of female cancers (13). There are approximately 8163 incident kidney cancers in England and Wales every year (13) of which 7347 are RCC. Of these patients, 27% and 14% are expected to have stage III and IV disease, respectively, and 33% of former stage I-II are expected to recur to stage III-IV, resulting in approximately 4456 patients diagnosed with advanced/mRCC per year (NICE TA169 (14, 15) updated with 2009 estimate from the British Association of Urological Surgeons (16)).

The risk of RCC increases with age; it is rare under the age of 50 and approximately two thirds of newly diagnosed cases are in patients over the age of 65 (17). The average age of diagnosis in the UK is 64 years (18). Other risk factors for RCC include smoking (19), overweight and obesity (20), hypertension (21), family history (22) and certain genetic mutations (e.g. mutations in the Von Hippel-Lindau (VHL) gene) (17).

Diagnosis, disease staging and prognosis

RCC is classified according to its histological subtype (e.g. clear cell) and stage. RCC is commonly staged using the American Joint Cancer Committee (AJCC) Tumour Node Metastasis (TNM) staging system. This staging system classifies the size of the tumour (T), the involvement of regional lymph nodes (N) and the presence of distant metastases (M). Advanced RCC, where the tumour is locally advanced or has spread to regional lymph nodes is classed as stage III. Metastatic RCC, where the disease has spread beyond the regional lymph nodes and to distant sites, is classed as stage IV (15). The most common sites of metastasis include lung and bone (23).

In many cases, RCC remains asymptomatic until it has reached an advanced stage (24) with up to one third of patients presenting with metastatic disease at the time of diagnosis (25). Any presenting symptoms can be diverse and can often be attributed to other things. Many tumours are often discovered incidentally when patients receive medical assessments for unrelated reasons (26).

HRQoL is negatively impacted in patients with advanced/mRCC and deteriorates when patients experience disease progression (27).

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is

otherwise indicated, in England and Wales and provide the source of the data.

- There are approximately 8163 newly diagnosed kidney cancers in England and Wales every year (13) of which 7347 are RCC.
- Approximately 4456 patients are diagnosed with advanced/mRCC each year.
- It is estimated that 68% of patients with advanced/mRCC are eligible for first-line therapy (based on the number of patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and patients eligible for immunotherapy) (15, 28).
- Approximately 77% of those eligible for first-line treatment will receive sunitinib (2333 patients) and approximately 5% cytokines (151 patients) (Pfizer, data on file).
- It is estimated that 64% of patients that received sunitinib or cytokines first-line would be eligible for second-line treatment with axitinib (Pfizer, data on file).
- Therefore approximately 1580 patients each year would be eligible to receive axitinib treatment (1484 having previously received sunitinib, and 96 having previously received cytokines).

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

The prognosis for advanced/mRCC is poor; the 5-year survival rate is approximately 10% (29). It is reported that UK patients survived approximately 4 months (median) once they have progressed following treatment with sunitinib (30, 31) and 10 to 13 months for patients who have been treated with cytokines or other agents used prior to the introduction of targeted therapy (32, 33). Life expectancy for these patients is expected to be substantially lower than the 24 months used by NICE to define end of life treatments.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

- In March 2009, NICE issued guidance (TA169) recommending sunitinib for the first-line treatment of advanced and/or metastatic RCC in patients who were suitable for immunotherapy and with an ECOG performance status of 0 or 1 (15).
- This was followed in August 2009 by guidance (TA178) based on a multiple technology appraisal (MTA), which recommended against the use of bevacizumab, sorafenib or temsirolimus for first line treatment and sorafenib or sunitinib for the second-line treatment of advanced and/or metastatic RCC (29).
- In February 2011, NICE issued guidance recommending pazopanib as a first-line treatment option for patients with advanced RCC who had not received prior cytokine therapy and with an ECOG performance status of 0 or 1 (TA215) (34).
- In April 2011, everolimus received a negative recommendation for the second-line treatment of patients with advanced RCC.

In summary, NICE recommends sunitinib or pazopanib for the first-line treatment of patients with advanced/mRCC with an ECOG performance status of 0 or 1. NICE does not currently recommend any interventional therapies for advanced/mRCC following failure of initial systemic therapy.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Surgical therapy is the only curative therapeutic approach for the treatment of localised RCC (12), however, a follow-up of patients who received radical nephrectomy for localised RCC revealed that nearly 30% had developed distant metastases after 5 years (35). Nephron-conserving surgery may be performed in patients with small tumours (18) or patients may receive partial or complete nephrectomy to remove the primary tumour (24). There is currently no evidence to support the use of adjuvant therapy following surgery (18, 36).

There is no cure for advanced/mRCC, therefore the goals of medical intervention are to extend life, prevent worsening of disease, relieve symptoms and maintain physical function (29). Advanced/mRCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy (29).

Traditional therapies for the systemic treatment of advanced/mRCC include the cytokines interleukin-2 (IL-2) and IFNα; however these treatments are associated with limited efficacy (only effective in certain subgroups of patients) and high toxicity (37, 38). However, due to a durable, complete response in a limited number of patients, high dose IL-2 can be considered as a monotherapy in patients with a good prognosis profile (12). Advances in the understanding of the molecular biology of RCC have led to the development of targeted therapies. Current targeted agents have focused on two pathways that are commonly de-regulated in RCC, the VEGFR pathway (e.g. sunitinib and pazopanib) and the mammalian target of rapamycin (mTOR) pathway (e.g. temsirolimus and everolimus).

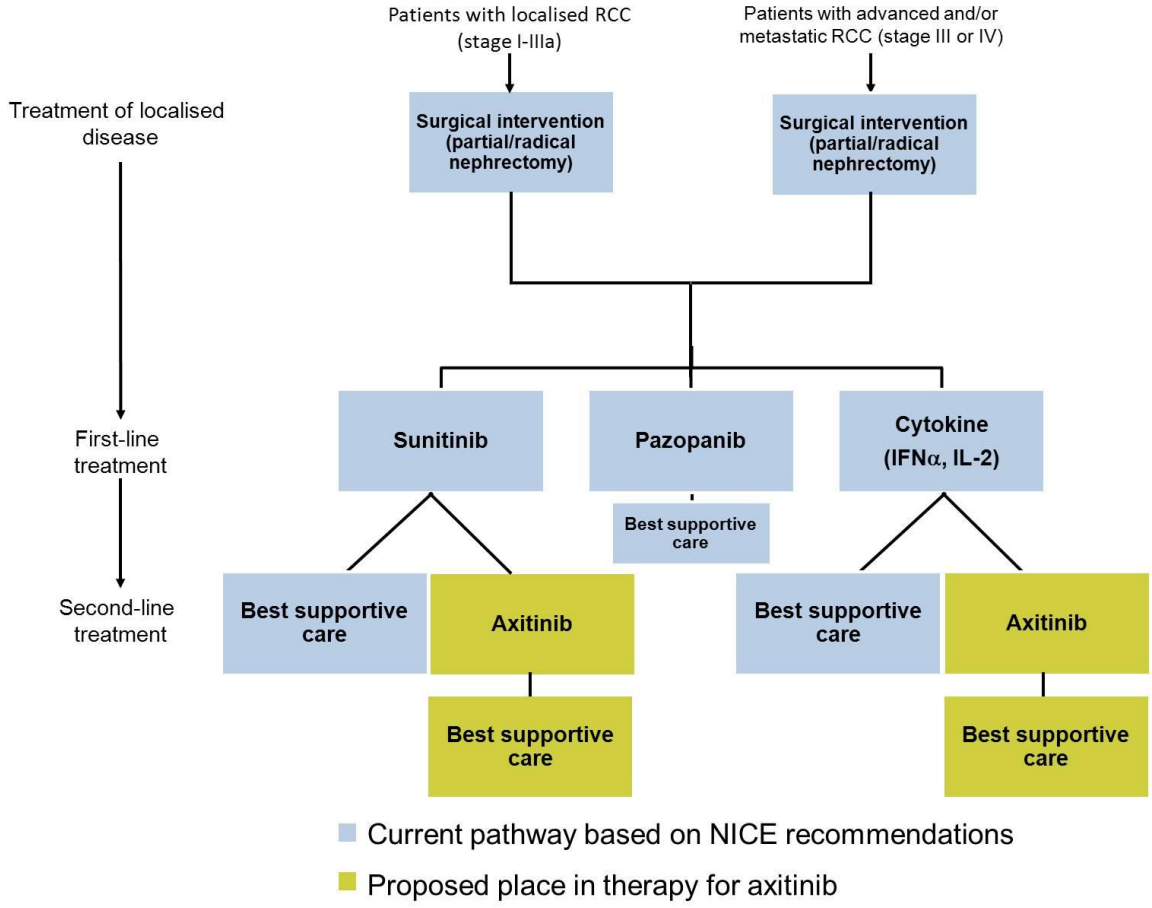
Current first-line treatment options in the UK include the TKIs, sunitinib and pazopanib, both of which have received a positive recommendation from NICE (15, 34). NICE does not currently recommend any interventional therapies for advanced/mRCC following failure of initial systemic therapy and patients subsequently receive BSC (defined as the provision of drug and non-drug therapy for the relief of symptoms and general patient management (39)).

The sequential use of VEGFR-TKI therapy for patients following progression on first-line VEGFR-TKI treatment is supported by a growing body of evidence from retrospective real-world analysis and Phase II studies. Efficacy results in the sunitinib refractory population in the AXIS trial further validates the clinical benefits of TKI to TKI sequencing in advanced/mRCC (40-44).

It is anticipated that axitinib will meet the unmet need for an effective second-line treatment after failure of sunitinib or a cytokine with an acceptable adverse event profile.

A proposed treatment pathway for patients with advanced/mRCC in England and Wales is provided in Figure 2, based on NICE guidance issued to date and the anticipated place in therapy of axitinib.

Figure 2: Proposed treatment pathway based on current NICE recommendations for patients with advanced/metastatic renal cell carcinoma (15, 24, 34)



2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

NICE recommends sunitinib or pazopanib for the first-line treatment of patients with advanced/mRCC. NICE does not currently recommend any interventional therapies for advanced/mRCC following failure of initial systemic therapy. The Cancer Drugs Fund, which was set up in 2011, allows patients in England to access therapies that may not have been approved by NICE (45). As a result, some patients in England, based on the recommendation of their treating physician, may currently be receiving everolimus as a second-line or third-line treatment in place of BSC. As the Cancer Drugs Fund only applies to England, the only option currently available in Wales is BSC as recommended by NICE.

Due to potential variations and uncertainties around the Cancer Drugs Fund, there exists an unmet need in both England and Wales for an effective pharmacological therapy recommended by NICE for the second-line treatment of advanced/mRCC to maintain patients' quality of life and extend overall survival.

2.7 Please identify the main comparator(s) and justify their selection.

There are no therapies currently recommended by NICE for second-line treatment of patients with advanced/mRCC for whom first-line therapy has failed (29). Therefore the main comparator in this submission is best supportive care (BSC) in line with the scope and current NICE guidance.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The most common adverse events experienced by axitinib treated patients in the Phase III trial have also been reported with other VEGF inhibitors. These were diarrhoea (54.9% of patients), hypertension (40.4% of patients) and fatigue (39.0% of patients). The most common Grade 3 AEs were hypertension (15.3% of patients), diarrhoea (9.7% of patients) and fatigue (9.5% of patients) (46). Diarrhoea can be managed with anti-diarrhoeal medications such as loperamide. Hypertension can be treated with standard anti-hypertensive therapies.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Axitinib will be taken at home by patients and therefore its administration will not incur any additional resource use.

Patients may require treatment for AEs associated with axitinib:

Diarrhoea: 10% of patients in the axitinib pivotal trial experienced Grade 3 or 4 diarrhoea (46)

- It is estimated that treatment would require two days of hospitalisation at a cost of £544 per episode[a].

Hypertension: 15.3% of patients in the axitinib pivotal trial experienced Grade 3 hypertension

- Treatment would require two GP visits per year (£53 per visit), two district nurse visits per year (£38 per visit) and anti-hypertensive medication (£273 per year; inflated to 2011 prices) (47).

2.10 Does the technology require additional infrastructure to be put in place?

It is not anticipated that any additional infrastructure will be required for the implementation of axitinib treatment.

[a] Code VC42Z Rehabilitation for other disorders

3 Equality

3.1 Identification of equality issues

3.1.1 *Please let us know if you think that this appraisal:*

- ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;***

- ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology***

- ***could lead to recommendations that have any adverse impact on people with a particular disability or disabilities***

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Not applicable.

3.1.2 *How has the analysis addressed these issues?*

Not applicable.

4 Innovation

4.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Advanced/mRCC exhibits a considerable burden to society and to patients. Despite recent advances in targeted therapies in first-line treatment, most patients' disease eventually progresses. The symptoms of metastatic disease, the various sites of metastases, and the generally poor prognosis associated with advanced/mRCC suggest that this disease has a substantial impact on survival and HRQoL, as well as on specific aspects such as physical functioning, energy and fatigue level, mental status, sexual functioning, and perceived well-being (48).

In the UK, the absence of an effective pharmacological therapy recommended by NICE for the second-line treatment of advanced/mRCC patients who have become refractory to first-line treatment, results in a very poor prognosis. It is estimated that the median survival of patients who progress from first line treatment with sunitinib was approximately 4 months in the UK (30, 31). In addition, as patients will be left untreated following failure of first line therapy, they are expected to rapidly progress and experience a significant deterioration in their HRQoL (49).

Axitinib is the first and only VEGFR-TKI proven to be superior over an active comparator in a purely second-line patient population. It has shown efficacy with statistically significant differences in progression free survival, with a manageable adverse-event profile that enables patients to maintain their HRQoL longer. Most importantly, in the pivotal Phase III study the median overall survival of patients with advanced/mRCC following failure of sunitinib or a cytokine was approximately 15 and 29 months respectively, suggesting a substantial life extension for patients who are at the end of life. Compared to BSC, axitinib is expected to offer substantial and significant health-related benefits, and so become a standard of care in second-line treatment of advanced/mRCC.

4.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

As described in Section 4.1, patients left untreated in the UK following failure of first line therapy, have a very poor prognosis and they are expected to rapidly progress and experience a significant deterioration in their HRQoL (49). As a result these patients at the end of their life are in a vulnerable state which is often characterised by worry, anxiety, sadness, and depression (50). The availability of axitinib is expected to offer a step change in second-line advanced/mRCC management by substantially improving survival compared to what is expected with best supportive care while maintaining HRQoL. HRQoL data from both the generic (non–disease-specific) instrument EQ-5D and the disease-specific FKSI-15 (and FKSI-Disease Related Symptoms subset) are suggestive that patients maintain their advanced/mRCC symptom "control", and more generally maintain their quality of life during treatment with axitinib (data presented in Section 6). Moreover, the knowledge that there is a treatment available provides patients

with renewed hope and optimism and may help alleviating the psychological burden associated with the disease.

4.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Evidence for responses to 4.1 and 4.2 are presented in Section 6.

5 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with advanced renal cell carcinoma who have received prior systemic treatment	Adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine	In line with the licensed indication
Intervention	Axitinib	As per scope	N/A
Comparator(s)	BSC	As per scope	N/A
Outcomes	Overall survival Progression free survival Response rates Adverse effects of treatment Health-related quality of life	As per scope	N/A
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.	As per scope	N/A
Subgroups to be considered	If evidence allows subgroups according to the following will be considered: • Prior treatment • Prognostic score (for example, ECOG or Motzer)	Subgroup analysis for adult patients with advanced/mRCC after failure of prior treatment with sunitinib or a cytokine	Whilst PFS for the total population of patients included in the AXIS trial has been sub-analysed by performance status, this analysis has not been conducted for the sub-population of patients after failure of prior treatment with sunitinib or a cytokine because the resulting sub-groups are too small for interpretable results

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Special considerations, including issues related to equity or equality	N/A	N/A	N/A

Abbreviations: BSC, best supportive care, ECOG, Eastern Cooperative Oncology Group; RCC, renal cell carcinoma.

Section B – Clinical and cost effectiveness

6 Clinical evidence

Key points

- Axitinib is the first VEGF-TKI proven to be superior over an active comparator in a purely second-line advanced/mRCC treatment setting.
- The efficacy and safety of axitinib for the treatment of patients with advanced/mRCC who had failed prior first-line systemic therapy has been demonstrated in a Phase III, randomised, active-controlled, international trial (AXIS) and three supporting Phase II, single-arm studies (42, 46, 51-53).
- The sunitinib refractory and cytokine refractory sub-populations form the main focus of this submission in line with the licensed indication. Results are presented in separate analyses for each subgroup as cytokine refractory patients are considered by many clinicians to comprise a different subgroup of patients compared with those who are sunitinib refractory.
- In the absence of head to head evidence for axitinib vs best supportive care (BSC; the comparator in the scope), an indirect comparison was performed to compare the relative efficacy of axitinib vs BSC in cytokine refractory patients and a simulated treatment comparison (STC) was performed to compare the relative efficacy of axitinib vs BSC in sunitinib refractory patients.

Efficacy of axitinib vs sorafenib

- Axitinib demonstrated significant improvements in progression-free survival (PFS) compared with sorafenib for patients who had failed first-line sunitinib and cytokine therapy in the Phase III pivotal trial (AXIS)
- In the sunitinib-refractory subgroup, median PFS in the axitinib arm was 4.8 months (95% CI, 4.5 to 6.4) compared with 3.4 months in patients treated with sorafenib (95% CI, 2.8 to 4.7 months) (HR=0.741; 95% CI, 0.573 to 0.958; p=0.0107)
- In the cytokine refractory subgroup, median PFS was 12.1 months (95% CI, 10.1 to 13.9 months) in the axitinib arm compared with 6.5 months (95% CI, 6.3 to 8.3 months) in the sorafenib arm (HR=0.464; 95% CI, 0.318 to 0.676; p<0.0001)
- In the sunitinib refractory subgroup, a numerically greater but not statistically significant number of axitinib treated patients (11.3%) achieved an objective response rate (ORR) compared with sorafenib treated patients (7.7%; p=0.1085). In the cytokine refractory subgroup, there was a statistically significant difference in the number of axitinib treated patients that achieved an ORR (32.5%) compared with sorafenib treated patients (13.6%; p=0.0002).
- Median overall survival in the axitinib arm was 15.2 months (95% CI: 12.8-18.3) in the sunitinib refractory subgroup and 29.4 months (95% CI: 24.5-NR) in the cytokine refractory group
- There was no significant difference between axitinib and sorafenib for median overall survival (OS) in the sunitinib refractory subgroup (HR=0.997, 95% CI: 0.782-1.270,

p=0.4902) or the cytokine refractory subgroup (HR 0.813, 95% CI 0.555-1.191, p=0.1435).

- Possible reasons for the lack of apparent OS benefit with axitinib vs. sorafenib despite the clear PFS benefit include the limitations of active comparator studies, the difficulty of demonstrating incremental OS benefit in advanced/mRCC, confounding due to long duration of survival post-progression and confounding due to post-study treatment.

Patient reported outcomes

- HRQoL as measured by Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI), FKSI-disease related sypmtoms (FKSI-DRS) and EuroQol-5D (EQ-5D) was maintained with both therapies while patients were on treatment, but declined when patients stopped study medication (mainly due to progression). As axitinib provides a greater PFS benefit than sorafenib, treatment with axitinib allows patients to maintain their HRQoL for longer.

Safety

- The pivotal Phase III trial (AXIS) demonstrated a distinct and generally manageable adverse event (AE) profile reflective of the mechanism of action of axitinib:
  - The most frequently reported AEs associated with axitinib treatment were diarrhoea (54.9%), hypertension (40.4%) and fatigue (39.0%).
  - In the axitinib arm, fewer patients experienced treatment-related AEs that led to permanent discontinuation (3.9%) compared with the sorafenib arm (8.2%).

Supporting clinical trial data

- Phase II data provides further evidence for the efficacy and safety in cytokine refractory and sorafenib refractory patients.

Statistical analyses: comparison with best supportive care

- Studies identified in the systematic review of RCTs were assessed for their suitability for inclusion into an indirect comparison of axitinib vs BSC in the sunitinib refractory and cytokine refractory patient populations. As these two populations differ markedly in their reponse to second line therapy, they are treated separately in the analysis in the subsequent sections.
- The link between axitinib and BSC was provided only by the TARGET trial, which compared the efficacy of sorafenib with placebo (used as a proxy for BSC). As the TARGET trial contained patients that had received first-line cytokine therapy only, the only comparison that could be made with sufficient methodological rigour was between axitinib and BSC in the cytokine refractory subgroup
- An indirect comparison of the sunitinib refractory population via the TARGET study would assume that a sunitinib refractory and cytokine refractory population are interchangeable. This assumption is implausible as clinicians consider a cytokine refractory population whom are TKI naïve to comprise a markedly different subgroup of patients compared with a sunitinib refractory population.
- A simulated treatment comparison (STC) was conducted to create an “adjusted” comparison between the axitinib sunitinib refractory population from AXIS and the

BSC prior-sunitinib population from RECORD-1.

- To supplement this analysis, OS hazard ratios from observational data for patients that received BSC or sorafenib following prior-sunitinib therapy were used in an indirect comparison to generate HRs for axitinib vs BSC in a sunitinib-refractory population.

Cytokine refractory patients

Results of indirect comparison

- For the PFS outcome, the hazard ratio for axitinib vs placebo in a cytokine refractory population was 0.251 (95% CrI 0.165-0.379), indicating that an axitinib treated patient has approximately a 75% reduction in the risk of progression compared with a placebo treated patient
- For the OS endpoint when the comparison was performed using the ITT population that were censored for cross-over in the TARGET trial, the hazard ratio was 0.63 (CrI 0.41-0.99), indicating a 37% reduction in the risk of death compared with a placebo treated patient.

Sunitinib refractory patients

Simulated treatment comparison

- In order to achieve a comparison of axitinib efficacy vs BSC in patients that received first-line sunitinib therapy, an STC was performed to estimate how sunitinib-refractory patients from the AXIS trial would have performed if they had been treated with placebo, using data from RECORD-1
  - For PFS using the ITT RECORD-1 placebo cohort, the estimated median PFS was 6.9 weeks (1.6 months) for axitinib-like patients if they had received placebo
  - For OS using the ITT RECORD-1 placebo cohort adjusted for cross-over using the rank preserving structural failure time (RPSFT) method, the estimated median OS was 36 weeks (8.3 months) for axitinib-like patients assuming that they received placebo.

Exploratory indirect comparison using observational data

- To support the results of the STC, a post-hoc analysis of real-world data from a Swedish patient registry (RENCOMP) was performed:
  - OS was compared amongst patients that had received first-line sunitinib followed by sorafenib or BSC and estimated hazard ratios were used in an indirect comparison to generate a hazard ratio for axitinib vs BSC in patients that had received prior-sunitinib
  - The estimated OS HR for axitinib vs BSC was 0.619 (95% CI 0.384-0.997).

6.1 Identification of studies

6.1.1 *Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.2, appendix 2.*

Two systematic reviews of the published literature were conducted to identify:

1) Randomised controlled trial (RCT) evidence on the efficacy and safety of axitinib and relevant comparators for the management of advanced/metastatic RCC (mRCC)
2) Non-RCT evidence on the efficacy and safety of axitinib only for the management of advanced/mRCC

The following section describes the methodology for the RCT and the non-RCT searches. Critical appraisals and descriptions of each relevant RCT and non-RCT are provided as requested in Section 10.3 (Appendix 3) and Section 10.7(Appendix 7), respectively.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), EMBASE (Ovid), The Cochrane Library and Web of Science were searched for relevant data.

In addition, the searches for relevant RCT data were supplemented by hand searching of conference proceedings for the American Society of Clinical Oncology (including the Genito-Urinary symposium), the European Society for Medical Oncology and the European Cancer Organisation. The Food and Drugs Administration website was also searched for Oncologic Drugs Advisory Committee reports.

Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for RCC, pharmacological intervention(s) of interest, and clinical trial design.

The search strategy for RCT evidence is provided in Section 10.2 (Appendix 2) and for non-RCT evidence in Section 10.6 (Appendix 6).

Of note, a third systematic review was performed as part of the work supporting the indirect comparison analysis. The aim of the review was to identify clinical studies (RCTs and non-RCTs) reporting efficacy and safety data in patients with advanced/mRCC who received BSC following progression with first-line sunitinib treatment.The methods and results of this sytemative review are provided in section 6.7.10 and section 10.15 (Appendix 15).

6.2 Study selection

6.2.1 *Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent.*

Studies identified (i1) were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded (e1), and allocated a “reason code” to document the rationale for exclusion. Papers included after this stage (i2) were then assessed based on

the full text; further papers were excluded (e2), yielding the final data set for inclusion (i3). The final included data set from the RCT search consisted of clinical studies for axitinib and those for comparator treatments. The full text of these comparator studies was screened and those suitable for indirect comparison were selected.

The final data set from the non-RCT search consisted of clinical studies for axitinib only. Inclusion and exclusion selection criteria for both SRs are shown in Table 2.

Table 2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	Adult patients with metastatic RCC who have received first- or second-line treatment.	Patients had received prior systemic therapy, as specified in the NICE scope.
Interventions	Any chemotherapy or targeted therapy in the second-line setting (RCT search only) Axitinib in the second-line setting (non-RCT search only)	In addition to the comparator stated in the scope (BSC), other interventions (both first and second-line) were searched in the systematic review. Studies where patients received a therapy as first-line treatment were later excluded for the purpose of this submission.
Outcomes	**Efficacy** • OS • PFS • TTP • ORR (complete + partial response) • Proportion of patients with stable disease • Duration of response • Time to response • Symptom assessments (where reported) • Time to deterioration (composite/individual endpoint) **Safety** Incidence and severity of AEs including, but not restricted to: • Incidence and severity (grade) of all reported AEs, e.g. hypertension • Withdrawals due to AEs • Incidence of serious AEs Quality of life or any other global patient-reported outcomes	Consistent with final scope

	Description	Justification
Study design	Prospective randomised controlled trials (for the RCT search) Non-RCTs (for the non-RCT search)	Separate searches were conducted for RCTs and non-RCTs
Language restrictions	English language only	To reduce number of hits and to identify studies in patient populations relevant to the UK setting
Exclusion criteria		
Population	Subjects <18 years of age	As specified by final scope
Interventions	Radiotherapy, surgery and other non-relevant comparators	Not relevant to final scope
Outcomes	Studies not investigating efficacy, safety or QoL	Not relevant to final scope
Study design	Non-RCTs (for the RCT search) RCTs (for the non-RCT search)	Separate searches were conducted for RCTs and non-RCTs
Language restrictions	Abstracts published in non-English language	To reduce number of hits and to identify studies in patient populations relevant to the UK setting

Abbreviations: AE: adverse event; BSC, best supportive care; NICE, National Institute for Health and Clinical Excellence; ORR, objective response rate; OS: overall survival; PFS: progression-free survival; QoL: quality of life; RCC: renal cell carcinoma; RCT: randomised controlled trial; TTP: time to progression

6.2.2 *A flow diagram of included and excluded studies at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses. Such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in Section 6.2.4.*

The RCT systematic review was conducted on 1 July 2010 and updated on 27 April 2012. Following assessment and exclusion of studies based on title, abstract and full text, 116 records representing 68 RCTs were identified. Of these 68 RCTs, 43 were excluded as they investigated treatments in the first-line setting.

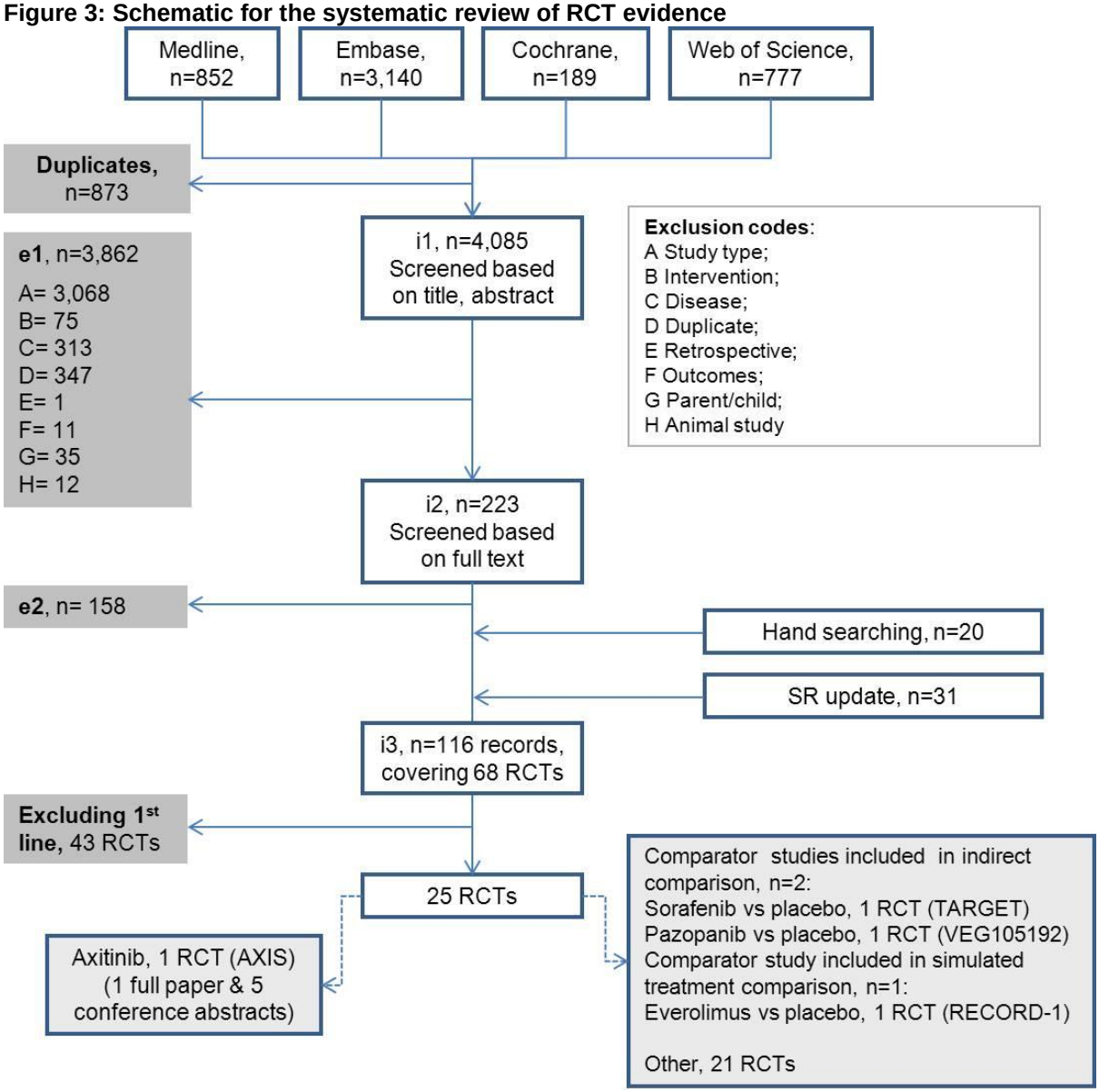
In total, 25 RCTs were included in the final data set of which:

- One RCT investigated the intervention of interest (axitinib): AXIS, for which there were six records identified (one full publication and five conference abstracts).
- 24 RCTs reported on comparator interventions

One of these RCTs, reporting on sorafenib vs BSC was eligible for indirect comparison/network meta-analysis. Details of this study are provided in Section 6.7.

The RCT systematic review schematic is shown in Figure 3.

Figure 3: Schematic for the systematic review of RCT evidence



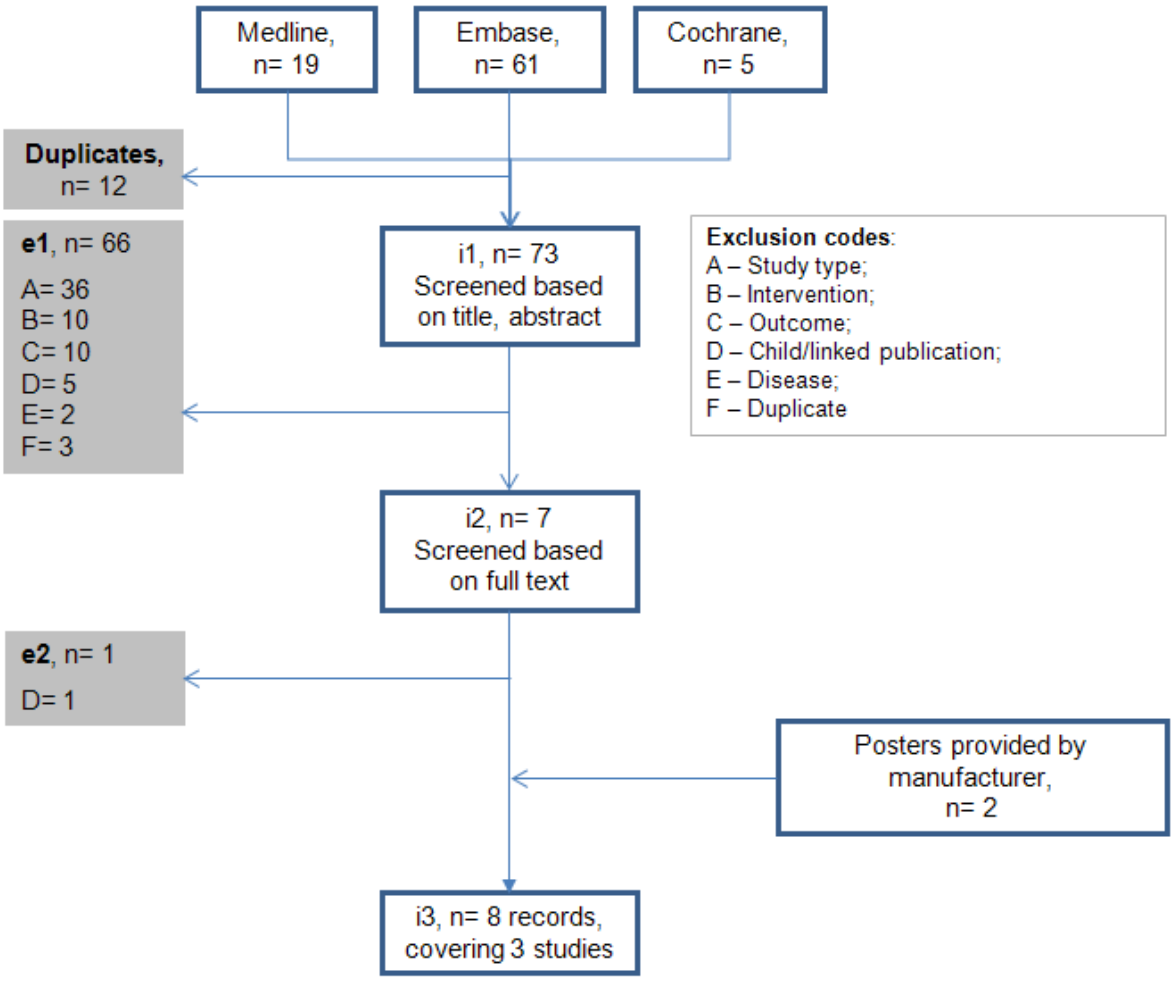
Abbreviations: RCT, randomised controlled trial; SR, systematic review.

Non-RCTs

The non-RCT systematic review was conducted on April 24th 2012. Following assessment and exclusion of studies based on title, abstract and full text, eight records covering three non-RCTs were identified. These are described in Section 6.2.7.

The systematic review schematic for the identification of non-RCT evidence is shown in Figure 4.

Figure 4: Schematic for the systematic review of non-RCT evidence for axitinib



6.2.3 *When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.*

One RCT for axitinib was identified from the systematic review: comparative efficacy of axitinib versus sorafenib in advanced/mRCC (AXIS): randomised Phase III trial. This RCT is described in detail in this submission. The primary sources of information for this RCT are Rini et al (2011) (51) and the clinical study report (CSR) (46). In addition the following were identified relating to the AXIS trial:

- A conference abstract (with corresponding presentation provided by Pfizer) of data from the AXIS trial (54, 55) which was superseded by the full RCT manuscript (51)
- Two conference abstracts on patient reported outcomes (with corresponding poster and presentation provided by Pfizer) (27, 56-58)
- A conference abstract of a post-hoc analysis of the effect of prior treatment regimen on treatment duration and titration (59) and the supporting presentation provided by Pfizer (60)

- A conference abstract (and presentation provided by Pfizer) on the association between polymorphisms on VEGF pathway genes and the relationship with progression-free survival (PFS) and blood pressure using data from the AXIS trial (61, 62).

In addition, the following were provided by the manufacturer:

- A supplementary report of final overall survival data (63)
- A supplementary report for patient reported outcomes (64)
- An abstract and poster presentation on updated efficacy and safety data from the cytokine refractory population presented at ASCO in June 2012 (after the date of the systematic review searches) (65).

Complete list of relevant RCTs

6.2.4 ***Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form.***

Table 3: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Objectives	Primary study ref.
Study A4061032 (AXIS) A Phase III, randomised, open-label, active-controlled, multicentre, international study (NCT00678392)	Axitinib 5mg BD taken orally, approximately 12 hours apart, administered in cycles of 4 weeks. Dose adjustment, at the discretion of the treating physician, including stepwise dose increase to 7 mg BD or 10 mg BD or dose reduction to 3 mg BD or 2 mg BD, were to be based on AEs experienced by the individual patient.	Sorafenib 400 mg (2 x 200 mg tablets) BD taken orally without food (at least 1 hour before or 2 hours after eating) approximately 12 hours apart, administered in 4-week cycles. Dose adjustments including dose reduction to 400 mg QD or QOD were permitted to manage suspected drug reactions.	Adult patients with mRCC) receiving axitinib or sorafenib following failure of a prior systemic first-line regimen containing one of the following: sunitinib, bevacizumab + IFNα, temsirolimus or cytokine(s).	***Primary objective:*** To compare PFS of patients with mRCC receiving axitinib or sorafenib following failure of one prior systemic first-line regimen containing one of the following: sunitinib, bevacizumab + IFNα, temsirolimus or cytokine(s), as assessed by the blinded IRC. ***Secondary objectives:*** To evaluate OS, ORR, duration of response, patient reported outcomes (FKSI and EQ-5D), TTD (a composite endpoint of time to death, disease progression or worsening of symptoms as measured by FKSI or FKSI-DRS) and safety.	CSR (46) and Rini et al, 2011 (51) Supplementary ref (63)

Abbreviations: AE, adverse event; BD, twice daily, mg, milligrams; EQ-5D, European quality of life-5 dimensions; FKSI, Functional Assessment of Cancer Therapy Kidney Symptom Index; FKSI-DRS, FKSI disease related symptoms; IFNα, interferon alpha; IRC, independent review committee; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; QOD, every other day; TTD, time to deterioration.

6.2.5 ***Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.***

The pivotal Phase III RCT (AXIS) compared axitinib with sorafenib for the second-line treatment of metastatic renal cell carcinoma. No RCTs were identified that compared axitinib

with best supportive care (BSC). To compare axitinib with BSC, the comparator provided in the NICE scope, an indirect comparison was performed. Due to limitations in the evidence network for axitinib vs BSC, a simulated treatment comparison (STC) and a database analysis were also performed. Full details of these analyses are provided in Section 6.7.

6.2.6 ***When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.***

No studies identified were excluded from further discussion.

List of relevant non-RCTs

6.2.7 ***Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in Section 6.8 and key details should be presented in a table.***

Three non-RCTs relevant to this submission were identified:

A4061012: A CSR and a corresponding publication were identified as the key data sources – these are summarised in Table 4.

Additional supporting data was identified:

- A publication reporting quality of life (QoL) data from A4061012 (66)
- A 5-year OS analysis (67).

A4061023: A CSR and corresponding publication were identified as the key data sources and are summarised in Table 4.

The following supporting data was identified:

- A post-hoc analysis of efficacy stratified by prior treatment regimen (68).
- A post-hoc analysis to determine the relationship between baseline FKSI (Functional Assessment of Cancer Therapy Kidney Symptom Index) score and PFS or OS (69)
- A combined post-hoc analysis of studies A4061012 and A4061023 to investigate the effect of levothyroxine on axitinib efficacy (70).

A4061035: A publication was identified for this non-RCT; this is summarised in Table 4.

Table 4: List of relevant non-RCTs

Trial no.	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
A4061012 A Phase II, open-label single-arm, multicentre, international study. (NCT00076011)	Axitinib 5 mg BD. Dose adjustment was permitted, including interruption, dose decrease or dose titration by 20% based on AEs.	Patients with mRCC who had previously received treatment with cytokines.	***Primary objective:*** To assess the response (ORR) to axitinib treatment as assessed by the Investigator. ***Secondary objectives:*** To evaluate duration of response, time-to-progression, OS, safety, PK and HRQoL.	Rixe et al, 2007 (52) and CSR (71) Supplementary ref: (67)	Provides supporting efficacy and safety evidence for axitinib in the population of relevance to the decision problem.
A4061023 A Phase II, open-label, single-arm, multicentre study. (NCT00282048)	Axitinib 5 mg BD. Dose adjustment was permitted, including stepwise dose titration to 7 mg BD and 10 mg BD, or dose reduction to 3 mg BD and 2 mg BD based on AEs.	Patients with sorafenib-refractory mRCC who had received one or more prior systemic treatments.	***Primary objective:*** To assess the response rate (ORR) to axitinib treatment as assessed by the Investigator. ***Secondary objectives:*** To evaluate safety, duration of response, PFS, OS and patient reported outcomes.	Rini et al, 2009 (42) and CSR (72)	Provides supporting efficacy and safety evidence for axitinib in the population of relevance to the decision problem.
A4061035 A Phase II, open-label, single-arm, multicentre study. (NCT00569946)	Axitinib starting dose of 5 mg BD	Patients in Japan who had received first-line cytokine treatment.	***Primary objective:*** To assess the response rate (ORR) to axitinib treatment according to the Investigator's assessment. ***Secondary objectives:*** PFS, duration of response, safety, biomarkers.	Tomita et al, 2011 (53)	Provides supporting efficacy and safety evidence for axitinib in the population of relevance to the decision problem.

Abbreviations: AE, adverse event; BD, twice-daily; HRQoL, health-related quality of life; mg, milligrams; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics.

6.3 Summary of methodology of relevant RCTs

6.3.1 ***As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.***

Methods

AXIS, the pivotal phase III axitinib trial, was the first head-to-head clinical trial in advanced/mRCC undertaken in a pure second-line population comparing axitinib against an active drug, sorafenib.

AXIS compared the efficacy and safety of axitinib with sorafenib.

6.3.2 ***Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.***

The methodology of the AXIS trial is summarised in Table 5.

Table 5: Methodology: AXIS (Study A4061032)

AXIS (Study A4061032)	**Details**
Study objectives	***Primary objective:*** To compare PFS of patients with mRCC receiving axitinib or sorafenib following failure of one prior systemic first-line regimen containing one of the following: sunitinib, bevacizumab + IFNα, temsirolimus or cytokine(s). ***Secondary objectives:*** To evaluate OS, ORR, duration of response, patient reported outcomes (FKSI and EQ-5D), TTD and safety.
Location	Conducted in 175 sites from 22 countries (Australia, Austria, Brazil, Canada, China, France, Germany, Greece, India, Ireland, Italy, Japan, Republic of Korea, Poland, Russian Federation, Singapore, Slovakia, Spain, Sweden, Taiwan, UK, and USA) (http://clinicaltrials.gov/ct2/show/NCT00678392). 49 patients at 10 centres in the UK were treated.
Design	A Phase III, randomised, open-label, multicentre, international, two-arm study conducted in 723 patients (361 axitinib, 362 sorafenib) with mRCC following failure of prior first-line systemic therapy.
Duration of study	The study began in September 2008. Treatment was to continue until disease progression, intolerable adverse drug reactions or withdrawal of consent. The final PFS analysis was conducted in June 2011. The final OS analysis was conducted on 1st November 2011.
Method of randomisation	Patients were randomised in a 1:1 ratio to receive either axitinib 5 mg BD or sorafenib 400 mg BD through a centralised registration and randomisation system (IVRS) using a permuted block design of size 4 (2 to axitinib and 2 to sorafenib) within each stratum. A web-enabled centralised registration system concealed treatment allocation before registration and allowed centres to enrol patients directly. Patients and investigators were not masked to study treatment. Patients were

AXIS (Study A4061032)	Details
	stratified based on ECOG performance status (0 vs 1) and by prior therapy (i.e. sunitinib-containing regimens vs bevacizumab-containing regimens vs temsirolimus-containing regimens vs cytokine-containing regimens).
Method of blinding	The study was open-label however the independent assessment of the primary endpoint (PFS) was done in a blinded manner by the IRC: Two independent reviewers read scans. Differences between the 2 independent reviewers were to be resolved by a third reviewer for final determination.
Intervention and comparator	Study treatment was to begin within 7 days of randomisation and was administered continuously in cycles of 4-weeks duration. Full details of available doses are provided in Table 6. **Axitinib (N=361)** • Administered at a starting dose of 5 mg BD • Doses were to be taken approximately 12 hours apart • Patients who tolerated axitinib with no AEs above CTCAE Grade 2 that were related to study drug for a consecutive 2 week period were eligible for a dose increase to 7 mg BD and then 10 mg BD (unless BP was >150/90 mmHg or the patient was receiving antihypertensive medication) at the discretion of the treating physician • Patients who developed an axitinib-related CTCAE Grade 1 or 2 had their dose continued at the same level • Patients with Grade 3 non-haematologic treatment-related toxicity† had their dose decreased by 1 level • Patients with Grade 4 non-haematologic treatment-related toxicity or Grade 4 haematologic toxicity‡ had their dose interrupted; they were restarted at 1 lower dose level as soon as improvement to CTCAE Grade ≤ 2. If the patient required dose reduction below 2 mg BD, the Sponsor was to be contacted for discussion before implementation. **Sorafenib (N=362)** • Administered at a starting dose of 400 mg BD taken orally, without food (at least 1 hour before and 2 hours after eating), 12 hours apart • Management of sorafenib-related drug reactions may have required dose interruptions and/or reduction • When dose reduction was necessary, the sorafenib dose may have been reduced to 400 mg QD • If additional dose reduction was required, sorafenib may have been reduced to a single 400 mg dose QOD Patients in both treatment arms that were removed from treatment due to intolerable toxicity continued to be followed after discontinuation.
Permitted and disallowed concomitant medications	No other chemotherapy or experimental anti-cancer medications were permitted during the on-study§ period. Any disease progression requiring other forms of systemic anticancer therapy was cause for discontinuation from study treatment. Palliative radiotherapy was allowed for pain control only to sites of bone disease present at baseline, and only following bone scan imaging demonstrating no new sites of bone metastasis. Palliative and supportive care for disease-related symptoms were permitted, including anti-diarrhoeal medications, anti-inflammatory or

AXIS (Study A4061032)	Details
	narcotic analgesics, diagnostic tests for fever or infection, antibiotics, therapeutic colony-stimulating factors, erythropoetic agents, blood transfusions and low dose oral steroids. ***Axitinib:*** The preferred treatment for patients requiring anticoagulant therapy was LMWH. Coumadin and coumarin derivatives were allowed; however, due to possibility of inhibition of CYP1A2-mediated metabolism of coumadin by axitinib, appropriate monitoring of prothrombin time/INR was required. Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (e.g. grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole,erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, delavirdine) were not permitted. Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (e.g. carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, St. John's Wort) were not permitted. Caution had to be exercised in patients receiving concomitant CYP3A4/5 inhibitors due to potential drug-drug interactions. Patients requiring chronic antacid therapy with histamine hydrogen antagonists, proton-pump inhibitors or locally acting antacids were required to stagger the timing of their axitinib and antacid dosing (patients were required to avoid the use of antacids for 2 hours before until 2 hours after taking axitinib. ***Sorafenib:*** Caution was recommended in the use of medications predominantly metabolised by the UGT1A1 enzyme. All concomitant medications were recorded.
Discontinuation of study therapy	Patients withdrew from the study for the following reasons: • Death • Unacceptable toxicity • RECIST disease progression (however, patients who had PD, but experienced clinical benefit from axitinib or sorafenib treatment were eligible for continued treatment provided that the treating physician assessed the risk/benefit of taking such an approach and that the SLD of measurable lesions was less than or equal to the baseline SLD per investigator and no alternative treatment was available) • Protocol deviation (after study start; including patient noncompliance) • Pregnancy • Patient choice to withdraw from treatment (follow-up permitted by patient) • Withdrawal of patient consent (cessation of follow-up)
Tumour assessments	Baseline tumour assessments required CT/MRI of the chest, abdomen, pelvis and brain along with a bone scan and were sent to the IRC. If the interval between any of the baseline tumour assessments and randomisation was >28 days, the baseline tumour imaging was repeated. At baseline, tumour lesions were categorized as target or non-target. All patients were evaluated for response according to RECIST. For all patients, CT/MRI (covering the same anatomy as the baseline scans, except brain) were required every 6 weeks for the first 12

AXIS (Study A4061032)	Details
	weeks, then every 8 weeks. If a baseline bone scan showed metastatic lesions, this was confirmed with concomitant x-ray, CT, MRI, and bone scans and bone imaging was required at the time points matched with CT/MRI evaluations (every 6 weeks for the first 12 weeks, and then every 8 weeks). Otherwise, sequential bone scans were not required unless clinically indicated according to the treating physician's judgment. All scans were sent to the IRC. CR or PR required confirmation with CT/MRI and a bone scan with concomitant imaging (the latter if baseline bone lesions were present) at least 4 weeks after the response was first noted. Tumour assessments were performed as scheduled until progression of disease or death, regardless of whether the patient was receiving study medication until permanent withdrawal from study treatment. The same method was used to characterise each identified and reported lesion at baseline and during the study period. If a patient developed new or worsening pleural effusion, or ascites that was large enough for thoracentesis or paracentesis, a fluid sample was obtained for cytological examination to determine whether the fluid collection was malignant, unless there was a reasonable clinical contraindication to do so. If fluid cytology was negative for malignant cells (including "negative", "atypical", or "indeterminate"), then the fluid collection alone was not to be used as evidence of PD. "PD" was assigned if fluid cytology was positive ("positive" or "malignant").
Primary outcome	Progression-free survival as assessed by the IRC – the scoring and timing of the primary endpoint is described in detail in Section 6.3.5.
Secondary outcomes	• PFS (Investigator assessment) • OS • ORR (IRC and Investigator assessed) • Duration of response (IRC and Investigator assessed) • Patient reported outcomes (FKSI, FKSI-DRS, EQ-5D and composite endpoint TTD) • Safety The scoring and timing of all secondary efficacy outcomes are described in detail in Section 6.3.5.
Duration of follow-up	Patients were followed until disease progression, intolerable adverse drug reactions or withdrawal of consent. The final assessment was performed 28 days after the last dose of study drug. All patients were followed for survival at least every 3 months after discontinuing study treatment until at least 3 years after randomisation of the last patient.

Abbreviations: BD, twice-daily; CR, complete response; CT, computed tomography; CTCAE, Common terminology criteria for adverse events; DR, duration of response; ECOG, Eastern Cooperative Oncology Group; EQ-5D, European Quality of Life 5D; FKSI, Functional Assessment of Cancer Therapy Kidney Symptom Index; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index -Disease Related Symptoms; INR, International normalised ratio; IRC, independent review committee; IVRS, interactive voice response system; LMWH, low molecular weight heparin; mRCC, metastatic renal cell carcinoma; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; QOD, every other day; RECIST, Response Evaluation Criteria in Solid Tumours; SLD, sum of longest diameters; TTD, time-to-deterioration.

† Patients who developed Grade 3 non-haematologic toxicities that were controlled with symptomatic medication or Grade 3 asymptomatic biochemistry laboratory abnormalities were to continue at the same dose level at the discretion of the investigator.

‡ Patients who developed Grade 4 lymphopenia or Grade 4 asymptomatic biochemistry laboratory abnormality may have continued study treatment without interruption.

§ The on-study period included the time from randomisation until 28-days after the final dose of study drug.

Dose adjustments

The starting dose of 5 mg BD was based on area under the curve results from studies that showed a near maximal decrease in blood flow/permeability and soluble VEGFR-2 in plasma. In addition, 5 mg BD was identified as the maximum tolerated dose in the first in-human study (73). Pharmacokinetic analysis demonstrated high inter-patient variability in achieving appropriate therapeutic levels with the 5 mg BD dose (73). A flexible dosing regimen was therefore developed to minimise the impact of inter-patient variability and allow patients to achieve adequate therapeutic exposure to axitinib via dose escalation or reduction based on individual tolerability. Within the AXIS study, the flexible dosing regimen included specific criteria based on individual tolerability for dose escalation and dose reduction across five dose levels (detailed in Table 5). For patients receiving sorafenib, only dose reductions were permitted as detailed in Table 5. Dose levels and formulations are presented in Table 6. The relative dose intensity was calculated as (actual total dose) / (intended total dose) × 100.

Table 6: Available study medication dose levels: AXIS (Study A4061032)

Dose level		Dose	Dispensed as
	Axitinib		
↑ +2	Dose escalation	10 mg BID	2 x 5 mg tablets BID
↑ +1	Dose escalation	7 mg BID	1 x 5 mg tablet BID + 2 x 1 mg tablet BID
0	Starting dose	5 mg BID	1 x 5 mg tablet BID
↓ -1	Dose reduction	3 mg BID	3 x 1 mg tablets BID
↓ -2	Dose reduction	2 mg BID	2 x 1 mg tablets BID
	Sorafenib		
0	Starting dose	400 mg BID	2 x 200 mg tablets BID
↓ -1	Dose reduction	400 mg QD	2 x 200 mg tablets QD
↓ -2	Dose reduction	400 mg QOD	2 x 200 mg tablets QOD†

Abbreviations: BD, twice daily, QD, once daily; QOD, every other day; † unlicensed dosing schedule.

Participants

6.3.3 *Provide details of the eligibility criteria (inclusion and exclusion) for the trial. Highlight any differences between the trials.*

The inclusion and exclusion criteria for the AXIS RCT are summarised in Table 7.

Table 7: Eligibility criteria – AXIS (Study A4061032)

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
A4061032 (AXIS)	• Histologically or cytologically confirmed mRCC with a clear cell subtype component • Evidence of uni-dimensionally measurable disease (i.e. ≥ 1 malignant tumour mass that could have been accurately measured in at least 1 dimension ≥ 20 mm with conventional CT	• Prior treatment of mRCC with more than 1 systemic first-line regimen • Previous treatment with any neoadjuvant or adjuvant systemic therapy • Major surgery <4 weeks or radiation therapy <2 weeks before starting study treatment. Prior palliative radiotherapy to metastatic lesion(s) was permitted, provided there was at least 1 measurable

Trial no. (acronym)	Inclusion criteria	Exclusion criteria

	scan or MRI scan, or ≥ 10 mm with spiral CT scan using a 5 mm or smaller contiguous reconstruction algorithm). Bone lesions, ascites, peritoneal carcinomatosis or miliary lesions, pleural or pericardial effusions, lymphangitis of the skin or lung, cystic lesions or irradiated lesions were not considered measurable
	• Progressive disease criteria per RECIST (Version 1.0) after 1 prior systemic first-line regimen for mRCC. The prior regimen had to have contained 1 of the following: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s)
	• Adequate organ function based on the following:
	  • Absolute neutrophil count ≥ 1500 cells/mm^3
	  • Platelet count ≥ 75,000 cells/mm^3
	  • Haemoglobin ≥ 9.0 g/dL
	  • AST and ALT ≤ 2.5 x ULN unless there were liver metastases, in which case AST and ALT ≤ 5.0 x ULN
	  • Total bilirubin ≤ 1.5 x ULN
	  • Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min
	  • Urinary protein <2+ by urine dipstick. If the dipstick was ≥ 2+, then a 24-hour urine collection could have been done and the patient could have entered only if urinary protein was <2 g per 24 hours.
	• Male or female ≥18 years (≥ 20 years in Japan)
	• ECOG performance status of 0 or 1
	• Life expectancy of ≥ 12 weeks
	• At least 2 weeks since the end of prior systemic treatment (4 weeks for bevacizumab + IFNα), radiotherapy or surgical procedure with resolution of all treatment-related toxicity to NCI CTCAE (version 3.0) Grade ≤ 1 or returned to baseline, except
		lesion that had not been irradiated
		• Gastrointestinal abnormalities including:
		  • Inability to take oral medication
		  • Requirement for intravenous alimentation
		  • Prior surgical procedures affecting absorption
		  • Treatment for active peptic ulcer disease in the last 6 months
		  • Active GI bleeding unrelated to cancer as evidenced by haematemesis, haematochezia or melena in the past 3 months without evidence of resolution
		  • Malabsorption syndromes
		• Current or anticipated need for treatment with known potent CYP3A4 inhibitors
		• Current or anticipated need for treatment with known CYP3A4 or CYP1A2 inducers
		• Requirement for anticoagulant therapy with vitamin K antagonists. Low dose anticoagulants for maintenance of patency of central venous access device or prevention of deep venous thrombosis were allowed. Therapeutic use of LMWH was allowed
		• Active seizure disorder or evidence of brain metastases, spinal cord compression or carcinomatous meningitis
		• A serious uncontrolled medical disorder or active infection that would have impaired the ability to receive study treatment
		• Any of the following within 12 months prior to study drug administration:
		  • Myocardial infarction
		  • Uncontrolled angina
		  • Coronary/peripheral artery bypass graft
		  • Symptomatic congestive heart failure
		  • Cerebrovascular accident
		  • Transient ischaemic attack
		  • VTE or PE (within the previous 6 months)
		• Known HIV or AIDS-related illness
		• History of a malignancy (other than RCC), except those treated with curative intent for skin cancer (other than melanoma), in situ breast or cervical cancers, or those treated with curative intent for any other cancer with no evidence of disease for 2 years
		• Dementia or altered mental status

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	for alopecia or hypothyroidism • No evidence of pre-existing, uncontrolled hypertension as documented by 2 baseline BP readings taken at least 1 hour apart. The baseline systolic BP readings had to be ≤ 140 mmHg and the baseline diastolic readings had to be ≤ 90 mmHg. Patients whose hypertension was controlled by hypertensive therapies were eligible. • Women of childbearing potential were required to have a negative serum or urine pregnancy test within 3 days before treatment	• Patients (male and female) not willing to employ an effective method of birth control during the study and for 6 months after discontinuation of treatment • Pregnant or lactating female patients • Other severe or acute chronic medical condition, psychiatric condition or laboratory abnormality that could have increased the risk associated with study participation or drug administration or interfered with the interpretation of the study results

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; HIV, human immunodeficiency virus; LMWH, low molecular weight heparin; mmHg, millimetres of mercury; mRCC, metastatic renal cell carcinoma; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PE, pulmonary embolism; RECIST, Response Evaluation Criteria in Solid Tumours; ULN, upper limit of normal; VTE, venous thromboembolism.

6.3.4 *Describe the patient characteristics at baseline. Highlight any differences between study groups.*

Patient demographics and characteristics at baseline are summarised in Table 8. There were no notable differences between the two treatment groups. The majority of patients in both treatment groups were <65 years of age and male. Age, race, geographic location, Eastern Cooperative Oncology Group (ECOG) score, and prior systemic therapy were similar between the two treatment groups. The two most common prior treatment regiments in both arms were sunitinib-containing regimens and cytokine-containing regimens (Table 8).

MSKCC risk groups were based on risk factors for previously treated subjects; Karnofsky performance status <80%, haemoglobin ≤13 g/dL for males and ≤11.5 g/dL for females, and corrected serum calcium >10 mg/dL. As Karnofsky performance status data were not collected in AXIS, mapping was performed to substitute Karnofsky performance status for ECOG performance status scores. An ECOG performance status (ECOG PS) of 0 was considered equivalent to a Karnofsky performance status ≥80% and an ECOG performance status of 1 was considered to be equivalent to a Karnofsky performance status <80% (Table 8).

Table 8: Patient demographics and baseline characteristics: AXIS (Study A4061032) – ITT population

Characteristic		Axitinib (N=361)	Sorafenib (N=362)
Age, years	Mean (SD)	59.7 (10.5)	60.0 (10.1)
	Median	61.0	61.0
	Min, max	20, 82	22, 80
	N	361	362
Age (years)	<65	238 (65.9)	238 (65.7)

Characteristic		Axitinib (N=361)	Sorafenib (N=362)
	≥ 65	123 (34.1)	124 (34.3)
Sex	Male	265 (73.4)	258 (71.3)
	Female	96 (26.6)	104 (28.7)
Race	White	278 (77.0)	269 (74.3)
	Black	1 (0.3)	4 (1.1)
	Asian	77 (21.3)	81 (22.4)
	Other	5 (1.4)	8 (2.2)
Geographic region	North America	88 (24.4)	98 (27.1)
	Europe	187 (51.8)	170 (47.0)
	Asia	73 (20.2)	79 (21.8)
	Other	13 (3.6)	15 (4.1)
ECOG performance status†	0	195 (54.0)	200 (55.2)
	1	162 (44.9)	160 (44.2)
	>1	1 (0.3)	0
MSKCC risk group‡	Favourable	100 (27.7)	101 (27.9)
	Intermediate	134 (37.1)	130 (35.9)
	Poor	118 (32.7)	120 (33.1)
	Not applicable	9 (2.5)	11 (3.0)
Previous systemic therapy	Sunitinib	194 (53.7)	195 (53.9)
	Cytokines	126 (34.9)	125 (34.5)
	Bevacizumab	29 (8.0)	30 (8.3)
	Temsirolimus	12 (3.3)	12 (3.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; mg, milligram; MSKCC, Memorial Sloan-Kettering Cancer Centre; SD, standard deviation;
† ECOG performance status was taken from case report forms and was the last measure obtained before dosing;
‡MSKCC risk groups were calculated based on the criteria for previously treated RCC patients.

Details of the disease history of the ITT population at baseline are presented in Table 9.

Table 9: Disease history –ITT population

Characteristic		Axitinib (N=361)	Sorafenib (N=362)
Histological classification, n (%)	Clear cell	355 (98.3)	359 (99.2)
	Other	1 (0.3)	0
	Not reported	5 (1.4)	3 (0.8)
Previous surgery for nephrectomy, n (%)	No	34 (9.4)	31 (8.6)
	Yes	327 (90.6)	331 (91.4)
	Unresected	3 (0.8)	1 (0.3)
	Resected	312 (86.4)	320 (88.4)

Characteristic		Axitinib (N=361)	Sorafenib (N=362)
	Partially resected	19 (5.3)	13 (3.6)
	Not found	1 (0.3)	2 (0.6)
	Not reported	5 (1.4)	2 (0.6)
Metastatic site, n (%)	Bone	119 (33.0)	107 (29.6)
	Pleural effusion	18 (5.0)	18 (5.0)
	Lung	274 (75.9)	292 (80.7)
	Lymph node	209 (57.9)	202 (55.8)
	Ascites	2 (0.6)	5 (1.4)
	Liver	102 (28.3)	103 (28.5)
	Pancreas	8 (2.2)	10 (2.8)
	Spleen	14 (3.9)	10 (2.8)
	Adrenal	77 (21.3)	60 (16.6)
	Kidney	81 (22.4)	77 (21.3)
	Pelvis	11 (3.0)	4 (1.1)
	Peritoneum	26 (7.2)	30 (8.3)
	Other	139 (38.5)	130 (35.9)

Outcomes

6.3.5 ***Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).***

As recognised in NICE guidance, the primary objectives of medical intervention for advanced/mRCC are the relief of physical symptoms and the maintenance of function (29). Consistent with this, the primary efficacy endpoint was progression-free survival (PFS), as determined by the blinded independent review committee (IRC). Secondary endpoints included PFS as determined by the Investigator, overall survival (OS), objective response rate (ORR), duration of response (DR), patient reported outcomes and AEs.

Primary outcome – Progression-free survival, Independent Review Committee assessment

The primary efficacy endpoint was PFS as measured by the IRC. PFS is considered to be a better surrogate marker of the true efficacy of a drug than OS for diseases where multiple lines of treatment are given (74) as it is not affected by any subsequent lines of therapy that

may be administered. In addition, there are several examples in the published literature that suggest there is an association between PFS and OS and that PFS may therefore serve as a surrogate endpoint for OS in advanced/mRCC. One study reported the results of a meta-analysis which showed a strong correlation (0.69) between PFS and OS. Results suggested that a 1-month difference in disease progression was associated with a 1.4-month difference in OS (75). This relationship was accepted by NICE in a previous appraisal (76). Another study of patients with advanced/mRCC that received targeted therapies reported that OS was shorter for those patients who progressed before 3 months compared with those who did not and similarly, OS was shorter for patients who progressed before 6 months compared with those who did not, thereby suggesting PFS is a surrogate endpoint for OS in patients with advanced/mRCC receiving targeted treatments (77, 78).

PFS was defined as the time from randomisation to first documentation of objective tumour progression or to death due to any cause, whichever occurred first. Tumour assessments were performed every 6 weeks for the first 12 weeks, and then every 8 weeks by calendar until disease progression or death, regardless of whether the patient was receiving study medication or until they had permanently withdrawn from the study.

Secondary outcomes

Progression-free survival, Investigator assessment: The same procedure was used as for the primary evaluation, but with PFS assessed by the Investigator.

Overall survival: OS is the gold standard marker of efficacy for any cancer treatment. However subsequent lines of active treatment, long survival post progression, or use of an active comparator, can all obscure the observed benefit on survival afforded by treatment being investigated (see Section 6.7.2). OS was defined as the time from the date of randomisation to the date of death due to any cause.

Objective response rate: ORR measures the degree of tumour shrinkage, which can result in a clinical benefit for patients. ORR was defined as the number of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST criteria. Patients who did not have on-study radiographic tumor re-evaluation or who died, progressed, or dropped out for any reason before reaching a CR or PR were counted as non-responders in the assessment of ORR. A patient who initially met the criteria for a PR and then subsequently became a confirmed CR was assigned a best response of CR.

Duration of response: Duration of response was defined as the time from the first documentation of tumour response (CR or PR) that was subsequently confirmed, to the first documentation of PD or death due to any cause, whichever occurred first. Patients who achieved a PR followed by a CR had times calculated using the date of PR as the first day. DR was only calculated for the subgroup of patients with a confirmed objective tumour response.

Table 10: Response Evaluation Criteria in Solid Tumours (RECIST)

Category	Definition
Complete response (CR)	Disappearance of all target and non-target lesions and no appearance of new lesions, documented on 2 occasions separated by at least 4 weeks.
Partial response (PR)	At least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum), without progression of non-target lesions and no appearance of new lesions; documented on 2 occasions separated by at least 4 weeks.
Stable disease (SD)	Measurements demonstrating neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify as PD. Non-target lesions may have persisted provided that there was no unequivocal progression in these lesions and no new lesions appeared.
Progressive disease (PD)	A ≥ 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, unequivocal progression of non-target lesions or the appearance of 1 or more new lesions. The occurrence of a pleural effusion or ascites was also considered PD if substantiated by cytological investigation and it was not previously documented. New bone lesions not previously documented were considered PD if confirmed by CT/MRI or X-ray.

Abbreviations: CT, computed tomography; LD, longest diameter; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial response.

Patient reported outcomes: Quality of life (QoL) was assessed using the 15-item Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) which measures symptoms and QoL in symptoms related to advanced kidney cancer disease. The total FKSI score is the sum of the 15 individual item scores[‡] (measured on a scale of 0 to 60) and the total FKSI-Disease Related Symptoms subset (measured on a scale of 0 to 36) (FKSI-DRS) is a subscale of nine individual scores which measure symptoms related to advanced kidney cancer disease including lack of energy, pain, losing weight, bone pain, fatigue, shortness of breath, coughing, bothered by fevers and haematuria. Higher FKSI scores indicate better QoL. In addition, generic health status was assessed using the EuroQoL-5D (EQ-5D) questionnaire. The EQ-5D consists of five domains of functional impairment: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Low scores represent a higher level of dysfunction.

Time to deterioration was assessed as a composite endpoint of death, disease progression or a FKSI-15 decrease of ≥ 5 points, whichever occurred first or defined as a composite measure of the time between date of death, disease progression, or a decrease of >3 points on the FKSI-DRS, whichever occurred first.

[‡] Each question on the FKSI questionnaire is answered on a 5-point Likert-type scale ranging from 0-4 (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). For some questions the answers are the item scores, for others the answers are reverse coded to create the item scores.

Statistical analysis and definition of study groups

6.3.6 ***State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).***

Population datasets analysed

Intent-to-treat (ITT): All patients who were randomised, regardless of whether they received study drug or received a different drug from that to which they were randomised. The ITT was the primary population for evaluating all efficacy endpoints as well as patient characteristics. In the AXIS trial, the ITT population was termed the full analysis set (FAS).

Safety analysis set (SAS): All patients who received at least one dose of study medication. The SAS was the primary population for evaluating treatment administration/compliance and safety.

Primary hypothesis, power calculation and sample size

The hypothesis was that treatment would result in an improvement in median PFS from 5 months with sorafenib based on previous clinical trial data (79, 80) to 7 months with axitinib.

The sample size was calculated based on 90% power to show improvement in PFS using a log-rank test with an overall 1-sided significance level of 0.025. The significance was calculated with the Lan-DeMets procedure with an O-Brien-Fleming stopping rule. Applying a randomisation of 1:1, a planned accrual period of 18 months and a follow-up period of approximately 5 months, it was estimated that 650 patients would need to be enrolled to observe 409 patients with disease progression or death by the end of the follow-up period. This assumed a 40% improvement in PFS from 5 months to 7 months in patients randomised to receive axitinib (as per the hypothesis) and non-uniform accrual (approximately 40% of patients enrolled at 9 months).

Other secondary and supportive analyses were tested at a significance level of 0.025 (1-sided test).

Censoring methods

PFS data were censored on the date of the last tumour assessment (on-study) documenting absence of PD for patients who:

- Were alive, on-study, and progression free at the time of the analysis
- Had at least one on-study disease assessment and discontinued treatment without documented disease progression and without death on-study
- For whom documentation of disease progression or death occurred after ≥ 2 consecutive missed tumour assessments (i.e. >12 weeks for the first 2 assessments and then subsequently >16 weeks after last tumour assessment
- Were given anti-tumour treatment, other than the study treatment, before documented disease progression.

Patients lacking an evaluation of their disease at baseline had their event time censored on the date of randomisation. Patients lacking an evaluation of tumour response after randomisation also had their event time censored on the date of randomisation unless death occurred prior to the first planned assessment (in which case the death was an event).

For OS, patients still alive at the time of the analysis had their OS time censored on the last date they were known to be alive. Patients lacking data beyond randomisation had their OS times censored at the date of randomisation.

Duration of response data were censored on the date of the last tumour assessment documenting absence of progressive disease for patients who:

- Were alive, on-study, and progression free at the time of the analysis
- Discontinued treatment without documented disease progression and without death on-study
- For whom documentation of PD or death occurred after ≥ 2 consecutive missed tumour assessments (i.e. >12 weeks for the first 2 assessments and then subsequently >16 weeks after last tumour assessment)
- Were given anti-tumour treatment, other than the study treatment, prior to documented disease progression.

Population included in primary analysis of primary outcome and methods for handling missing data

The primary outcome (PFS) was compared between the axitinib and sorafenib treatment groups in the ITT population.

PFS data were censored on the date of the last tumour assessment (28 days after the final dose of medication) documenting absence of progressive disease for patients. For details of the methods for handling missing data, please refer to the above section (censoring methods).

Statistical tests in primary analysis of primary outcome

PFS was summarized for the ITT (i.e. all patients that were randomised) using Kaplan-Meier methods and displayed graphically, where appropriate. The median event time for each treatment arm and corresponding 2-sided 95% CI were provided for PFS. The HR and 95% CI were estimated. A stratified (by ECOG PS and prior therapy) log-rank test (1-sided, α=0.025) was used to compare PFS between the two treatment arms.

Secondary statistical analyses

An unstratified log-rank test (1-sided, α=0.025) and Cox regression model were also used as secondary analyses for PFS. Cox regression models were used to explore the potential influences of the stratification factors on the primary endpoint. In addition, the potential influences of baseline characteristics (e.g. age, ethnic origin, sex, geographic region, MSKCC risk group) on the primary PFS endpoint were evaluated. For each treatment arm, the median PFS and a 2-sided 95% CI were provided for each level of the stratification variables.

The stratified log-rank test (1-sided, α=0.025) was used to evaluate the primary efficacy endpoint, PFS, in the SAS (i.e. all patients who received at least 1 dose of study medication).

The number and % of patients achieving objective response (CR or PR) were summarised along with the corresponding exact 2-sided 95% CI calculated using a method based on the F distribution. A Pearson χ^2 test (unstratified) and a Cochran-Mantel-Haenszel test stratified by baseline stratification factors were used to compare ORR between the 2 treatment arms. For the unstratified analyses, point estimates of the rates for each treatment arm and difference of the rates between treatment arms were provided, along with the corresponding 2-sided 95% CIs, using an exact method based on the F distribution and using a normal approximation for constructing a CI for differences, respectively. For the stratified analyses, the relative risk ratio estimator was used to contrast the treatment effects on the endpoint. Both a point estimate and a 2-sided 95% CI were calculated using a normal approximation.

Time-to-event endpoints, including OS and DR, were summarized using Kaplan-Meier methods and displayed graphically where appropriate. DR was calculated for the subgroup of patients with objective disease response. An unstratified and stratified log-rank test (1-sided, α=0.025) was used to compare OS between the 2 treatment arms. The median event time and 2-sided 95% CI for the median were provided for each endpoint. The HR and its 95% CI were estimated for OS. Additionally for each treatment arm, the median OS and a 2-sided 95% CI were provided for each level of the stratification variables. For DR, if the number of patients experiencing CR and PR was small, thereby limiting use of the Kaplan-Meier method to provide reliable information, descriptive statistics or listings were to be provided.

6.3.7 *Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.*

Pre-planned analyses of the primary efficacy endpoint were performed for the stratification factors ECOG PS (0 and 1) and prior treatment regimen (sunitinib-containing regimen, bevacizumab-containing regimen, temsirolimus-containing regimen, and cytokine-containing regimen). In addition, pre-planned subgroup analyses were performed on the primary efficacy endpoint for the baseline patient characteristics of age (<65 years, ≥ 65 years), sex (male, female), ethnic origin (white, non-white), geographic region (Asia, Europe, North America, Other) and MSKCC risk group (favourable, intermediate, poor).

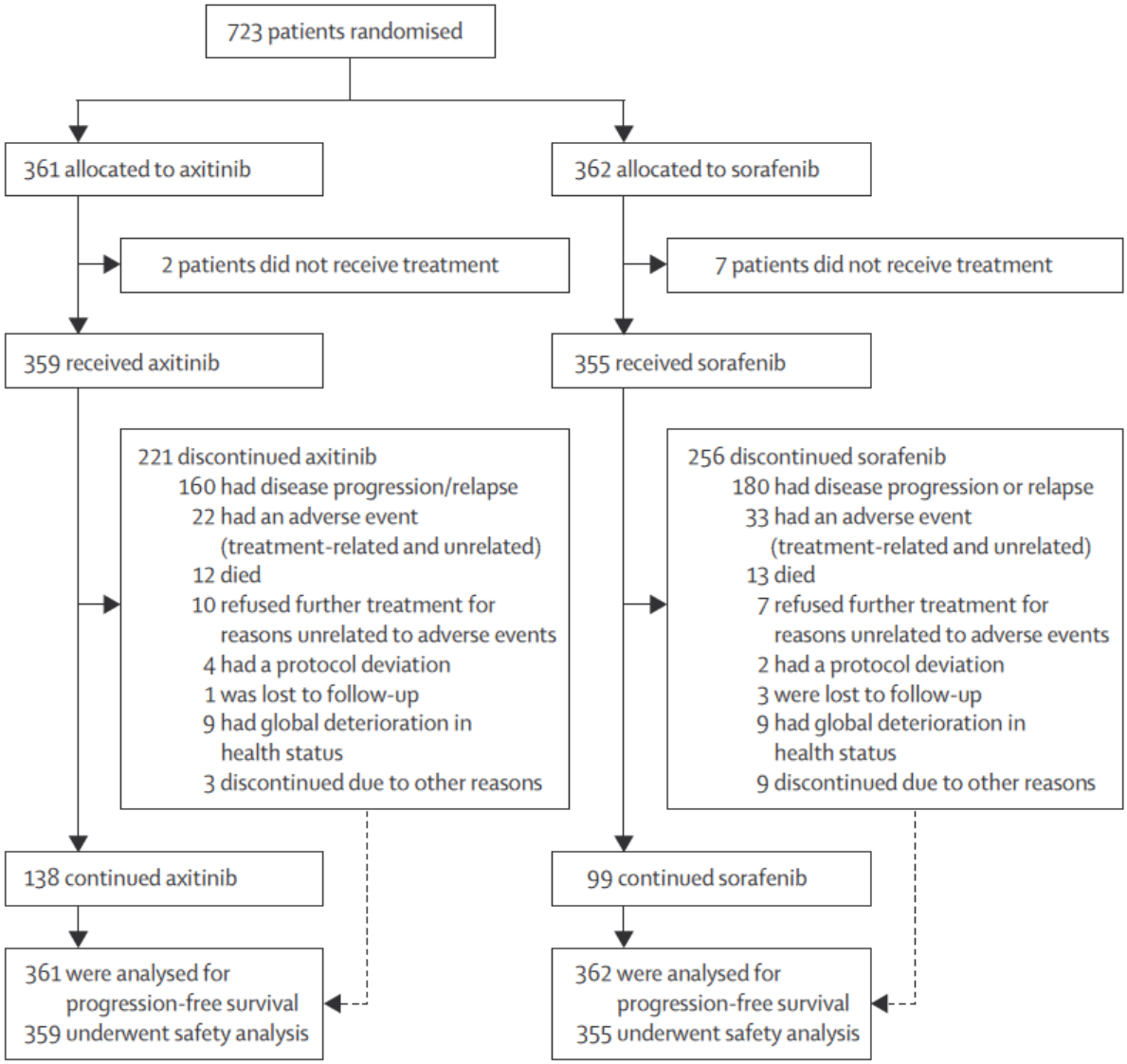
Pre-planned analyses of secondary efficacy endpoints, including OS, ORR and DR, were performed for the stratification factors ECOG PS (0 and 1) and prior treatment regimen (sunitinib-containing regimen, bevacizumab-containing regimen, temsirolimus-containing regimen, and cytokine-containing regimen).

Participant flow

6.3.8 *Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.*

A CONSORT flow chart showing the number of patients who were eligible to enter the AXIS trial, and who were randomised and allocated to each treatment are presented in Figure 5.

Figure 5: Participant flow: AXIS (Study A4061032)



6.3.9 *Treatment exposure*

Overall, patients randomised to receive axitinib had more median days on treatment and fewer discontinuations due to AEs compared with patients that received sorafenib (Table 11).

A flexible dosing regimen was permitted for patients to minimise the impact of inter-patient variability and allow patients to achieve adequate therapeutic exposure to axitinib according to the specific criteria for dose escalation and dose reduction based on individual tolerability

detailed in Table 5. Patients receiving sorafenib were permitted to receive dose reductions only as detailed in Table 5.

Table 11: Summary of study drug exposure – AXIS (Study A4061032) - SA set

Treatment exposure	Axitinib N=359	Sorafenib N=355
Days on treatment†		
Mean (SD)	220.8 (148.8)	180.7 (135.9)
Median (range)	196.0 (1, 670)	152.0 (1, 610)
Patients with AEs leading to discontinuation, n (%)	33 (9.2)	46 (13.0)
Relative dose intensity†† (%)		
Mean (SD)	102.0 (35.2)	80.1 (22.0)
Median (range)	98.6 (32.4, 194.4)	91.7 (26.7, 100.0)

Abbreviations: AE, adverse event; SAS, safety analysis set; SD, standard deviation.
†Days on treatment was the period from the first dose to the last dose; ††Relative dose = (actual total dose) / (intended total dose) × 100 .

Patients who discontinued study medication may have received subsequent therapy based on the judgement of the treating physician (63). In the cytokine-refractory subgroup, 46.4% of patients in both the axitinib arm and in the sorafenib arm received subsequent treatment. In addition, 22.7% of patients in the axitinib arm and 20.0% of patients in the sorafenib arm received more than 1 subsequent treatment. In the sunitinib-refractory subgroup, 65.2% of patients in the sorafenib arm and 60.0% of patients in the axitinib arm received subsequent treatment. Additionally, 28.6% of patients in the axitinib arm and 33.2% of patients in the sorafenib arm received more than 1 subsequent treatment.

6.4 Critical appraisal of relevant RCTs

6.4.1 ***The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies.***

6.4.2 ***Please provide as an appendix a complete quality assessment for each RCT. See Section 10.3, appendix 3 for a suggested format.***

A critical appraisal of the AXIS study is presented in Section 10.3 (Appendix 3).

6.4.3 ***If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.***

A summary is not required as there is only one relevant RCT.

6.5 Results of the relevant RCTs

6.5.1 ***Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients***

provided. If patients have been excluded from the analysis, the rationale for this should be given.

6.5.2 ***The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.***

6.5.3 ***For each outcome for each included RCT, the following information should be provided.***

The unit of measurement.

- ***The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio in an equivalent statistic. Both absolute and relative data should be presented.***
- ***A 95% confidence interval.***
- ***Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.***
- ***When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.***
- ***Other relevant data that may assist in the interpretation of the results may be included, such as adherence to medication and/or study protocol.***
- ***Discuss and justify definitions of any clinically important differences.***
- ***Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.***

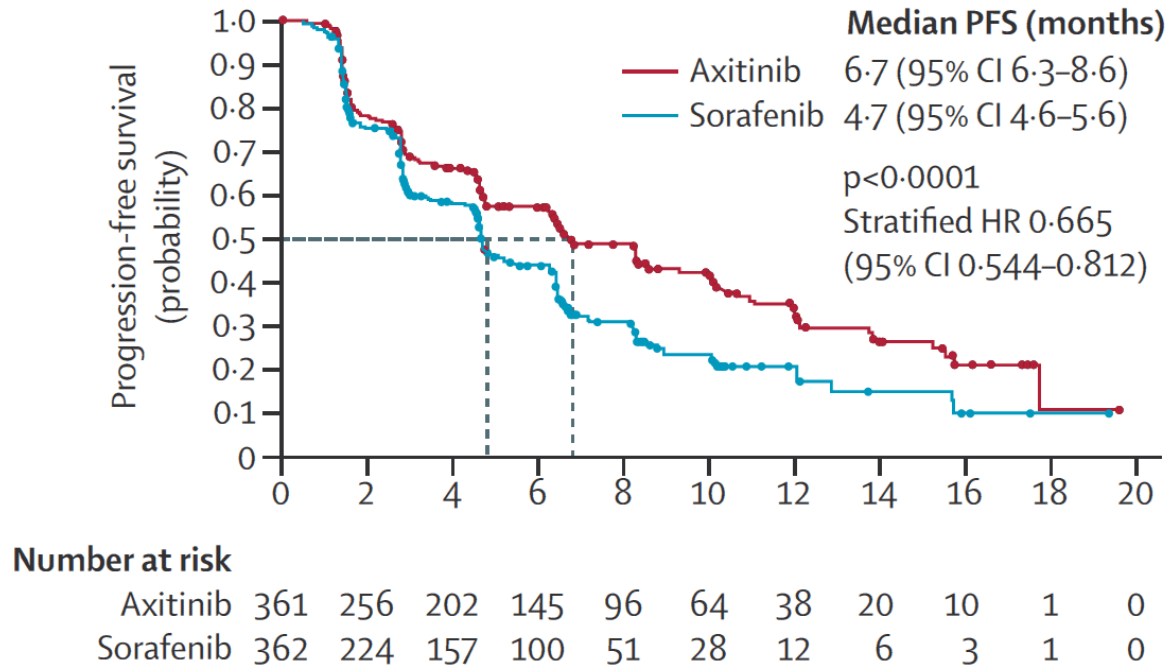
6.5.4 ***Results: AXIS (A4061032)***

Primary efficacy outcome: Progression-free survival, IRC assessment (ITT population)

Primary analysis

At the time of the final PFS analysis, a total of 402 patients out of the 723 patients that were randomised had experienced disease progression or death as assessed by the blinded IRC. In total, 192 (53.2%) patients in the axitinib arm and 210 (58.0%) patients in sorafenib arm had a PFS event. The median PFS was 6.7 months (95% CI [6.3, 8.6]) for axitinib treated patients compared with 4.7 months (95% CI [4.6, 5.6] for sorafenib treated patients. The observed hazard ratio (HR) was 0.665 (axitinib vs sorafenib; 95% CI [0.544, 0.812]) with a 1-sided p-value <0.0001, adjusted for ECOG PS and prior treatment regimen. Kaplan-Meier curves for PFS based on the analysis of the overall (ITT) population are presented in Figure 6.

Figure 6: Kaplan-Meier estimated median PFS for all patients treated with axitinib or sorafenib (ITT population)



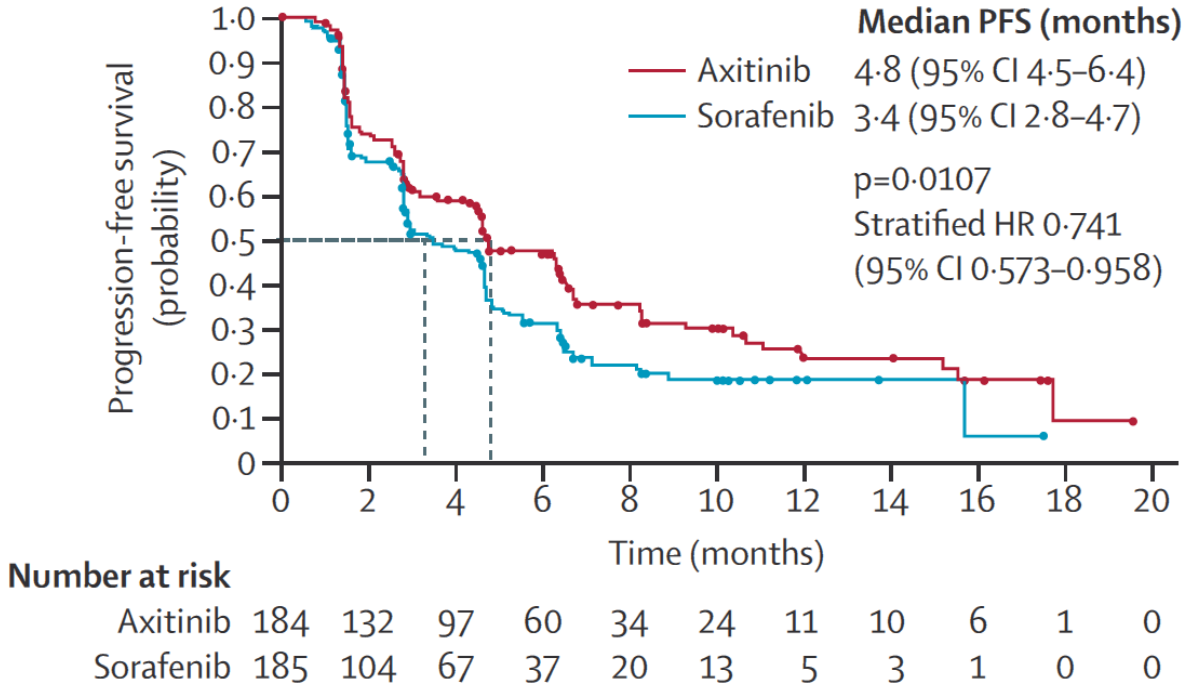
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Stratification by prior treatment regimen

As sunitinib-refractory and cytokine-refractory patients are considered to comprise separate populations, the main body of the analysis has been conduducted based on these two subgroups.

Prior sunitinib-containing regimen: Overall stratified analysis: Based on the IRC assessment of patients stratified by prior sunitinib-containing regimen, 60.3% of axitinib treated patients and 61.5% of sorafenib treated patients had a PFS event. The median PFS in the axitinib arm was 4.8 months (95% CI [4.5, 6.4]) and 3.4 months (95% CI [2.8, 4.7]) in the sorafenib arm. The HR was 0.741 (axitinib vs sorafenib; 95% CI [0.573, 0.958]) with a p-value of 0.0107 based on a 1-sided log-rank test stratified by ECOG PS (i.e. a 25.9% reduction in the hazard of disease progression or death) (Figure 7).

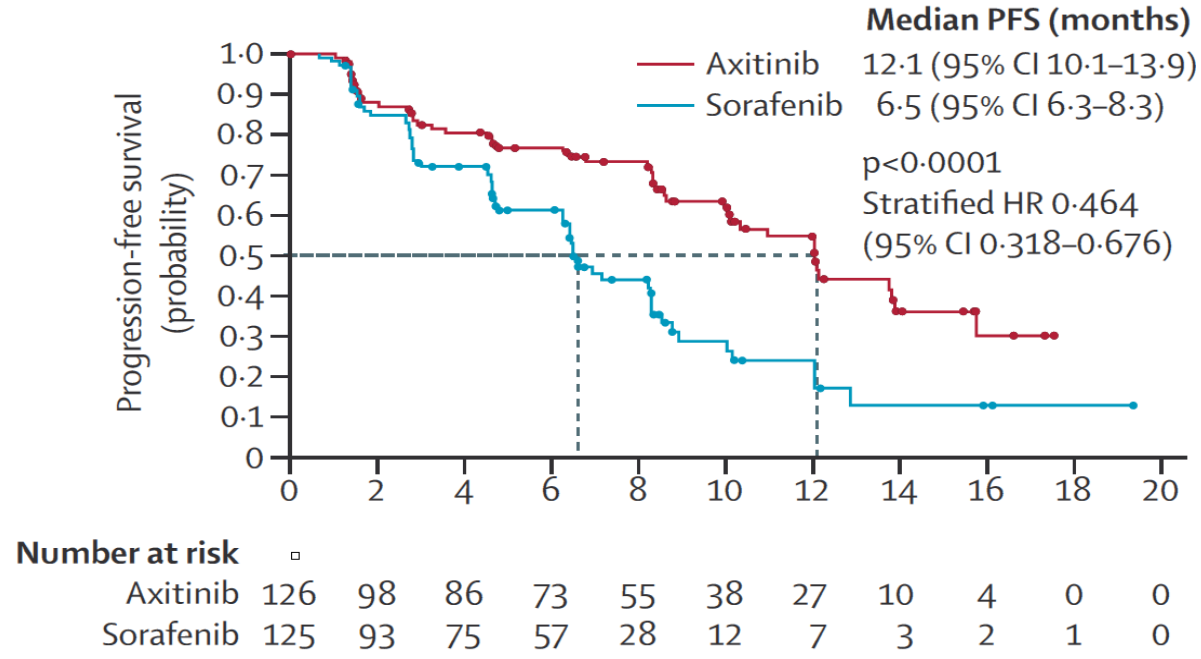
Figure 7: Kaplan-Meier estimated median PFS for patients previously treated with a sunitinib-containing regimen (ITT population)



Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Prior cytokine-containing regimen: Based on the IRC assessment of patients stratified by prior cytokine- containing regimen, 39.7% of axitinib treated patients and 55.2% of sorafenib treated patients experienced a PFS event. The median PFS was 12.1 months (95% CI [10.1, 13.9]) in the axitinib arm and 6.5 months (95% CI [6.3, 8.3]) in the sorafenib arm. The HR was 0.464 (axitinib vs sorafenib; 95% CI [0.318, 0.676]) with a p-value of <0.0001 based on a 1-sided log-rank test stratified by ECOG PS (i.e. a 53.6% reduction in the hazard of disease progression or death) (Figure 8).

Figure 8: Kaplan-Meier estimated median PFS for patients previously treated with a cytokine-containing regimen (ITT)



Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Presentation of PFS estimates based on prior bevacizumab- and temsirolimus-containing regimens are not presented, since very low numbers of patients received these first-line treatments (8.2% and 3.3%, respectively), resulting in wide confidence intervals and therefore making it difficult to draw firm conclusions. The licensed indication for axitinib does not include prior-bevacizumab and prior-temsirolimus patients and these populations therefore fall outside the scope of this appraisal.

Sensitivity analyses on the PFS primary endpoint

The robustness of the treatment effect of axitinib on PFS was examined by performing multiple sensitivity analyses. These included:

- Analysis to correct for potential bias in follow-up schedules
- Analysis to include patients who were discontinued due to deteriorating health status prior to progression of disease as per RECIST as events
- Analysis to correct for any bias from various censoring rules, such as discontinuation without progression, missed tumour assessments and the start of subsequent anti-tumour treatment, by treating these as events
- Analysis to include, as events, patients who were discontinued when progression was observed by the Investigator and subsequent scans were thus unavailable for IRC assessment
- Analysis to check for consistency of treatment effect in the SAS population.

The sensitivity analyses consistently showed that axitinib offered a statistically significant and clinically relevant benefit vs sorafenib in the overall population the sunitinib-refractory and the cytokine refractory subgroups, thus supporting the primary analysis (data not shown).

Secondary efficacy outcome: progression-free survival, Investigator assessment (ITT population)

A summary of PFS as assessed by the Investigator is presented in Table 12 for the overall stratified analysis as well as the sunitinib-refractory and cytokine-refractory populations.

Table 12: Summary of progression-free survival as assessed by the Investigator (ITT population)

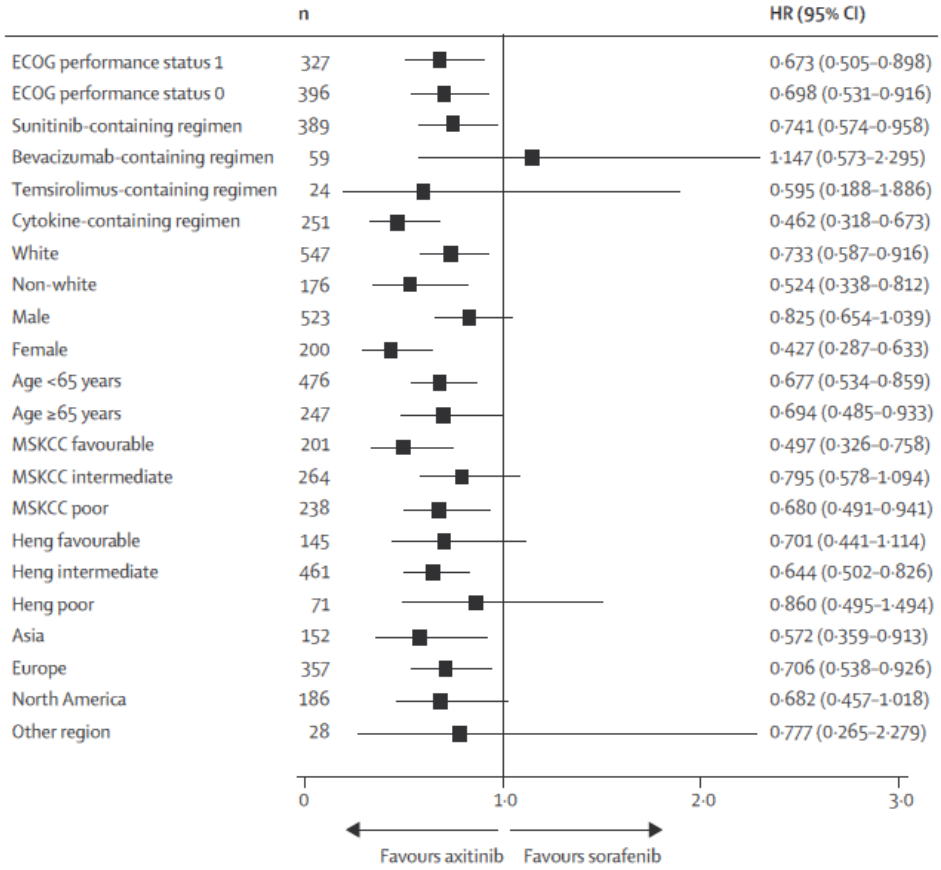
	Axitinib N=361	Sorafenib N=362
Overall stratified analysis (n)	**361**	**362**
Patients observed to have PFS event during study†, n (%)	201 (55.7)	227 (62.7)
Kaplan-Meier estimate of time to event (months), 50% quartile (95% CI)	8.3 (6.6, 9.0)	5.6 (4.7, 6.5)
Axitinib vs sorafenib HR‡ (95% CI)	0.658 (0.543, 0.798)	
p-value	<0.0001	
Prior sunitinib-containing regimen subgroup (n)	**194**	**195**
Patients observed to have PFS event during study†, n (%)	120 (61.9)	129 (66.2)
Kaplan-Meier estimate of time to event (months), 50% quartile (95% CI)	6.5 (4.8, 7.6)	4.5 (3.0, 4.7)
Axitinib vs sorafenib HR‡ (95% CI)	0.636 (0.494, 0.818)	
p-value	0.0002	
Prior cytokine-containing regimen subgroup (n)	**126**	**125**
Patients observed to have PFS event during study†, n (%)	57 (45.2)	74 (59.2)
Kaplan-Meier estimate of time to event (months), 50% quartile (95% CI)	12.0 (10.1, 13.8)	8.3 (6.6, 9.9)
Axitinib vs sorafenib HR‡ (95% CI)	0.636 (0.449, 0.900)	
p-value	0.0049	

Abbreviations: CI, confidence interval; HR, hazard ratio ITT, intent-to-treat.
†The study period included treatment plus a 28-day follow-up; ‡Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favour of axitinib; a hazard ratio >1 indicated a reduction in favour of sorafenib.

Secondary efficacy outcome: progression-free survival by individual baseline factor (IRC)

A Forest plot of HR for subgroup comparisons of demographic and other baseline characteristics is presented in Figure 9. The HR was <1, i.e. favouring axitinib in all subgroups with the exception of the prior bevacizumab-containing regimen, which had a wide CI due to the small number of patients in that group. Other subgroups containing small numbers of patients had wide CIs, for example the temsirolimus-containing regimen subgroup and the 'other' geographical location subgroup. Subgroup analyses of PFS based on age, sex, MSKCC risk categories and region showed a consistent advantage with axitinib.

Figure 9: Cox proportional analysis of progression-free survival; treatment comparisons controlling for individual baseline characteristics, IRC assessment (ITT population)



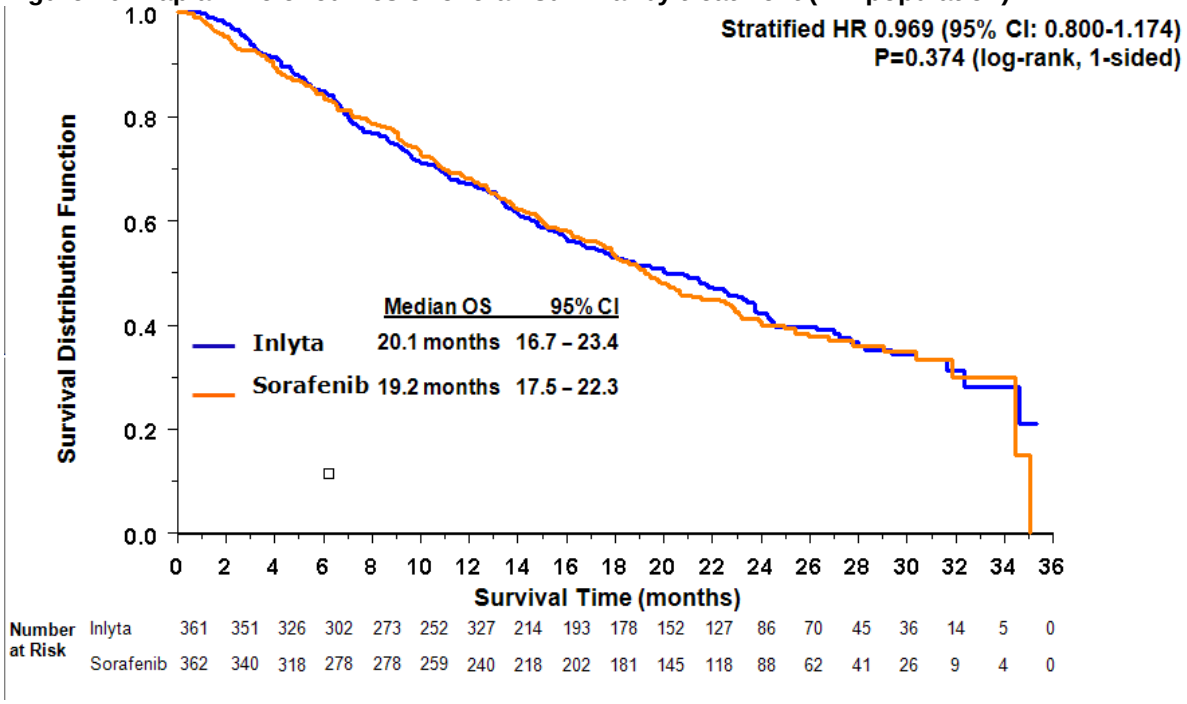
Abbreviations: CI, confidence interval; ECOG, Easter Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; MSKCC, Memorial Sloan-Kettering Cancer Centre

Secondary efficacy outcome: Overall survival (ITT population)

At the time of the final PFS analysis, only 223 of 723 patients had died (approximately 30% of the total number enrolled and 50% of the required 417 events for the final OS analysis). The final OS analysis was performed on 1st November 2011 (63).

At this time, there were 211 deaths (58.4%) in the axitinib arm and 214 deaths (59.1%) in the sorafenib arm of the ITT population. The observed HR was 0.969 (95% CI [0.800, 1.174]) with a 1-sided p-value of 0.3744 adjusted for ECOG PS and prior treatment regimen. The Kaplan-Meier curve for OS in the overall study population is presented in Figure 10.

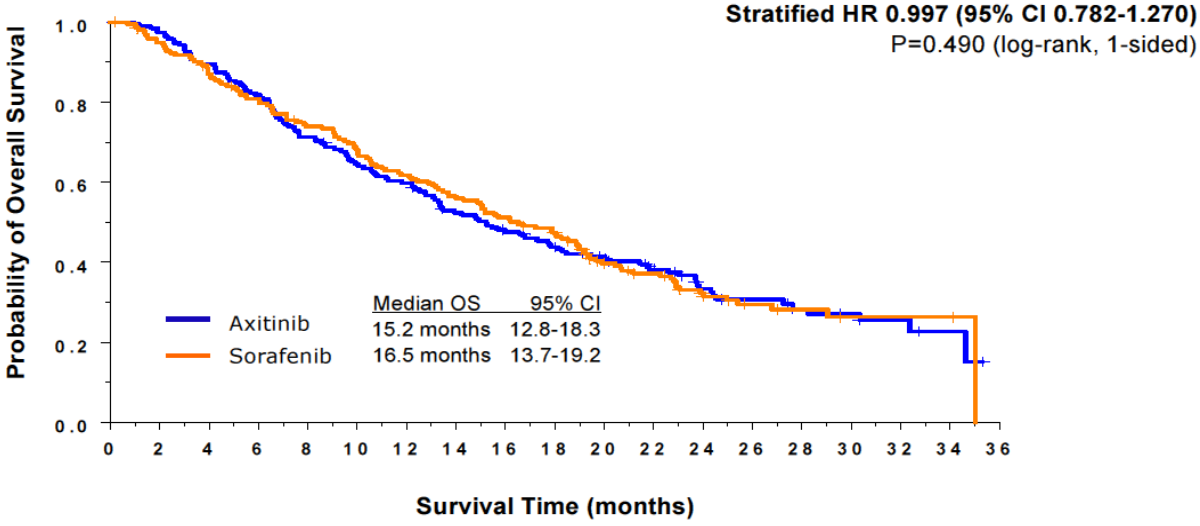
Figure 10: Kaplan-Meier curves of overall survival by treatment (ITT population)



Abbreviations: CI, confidence interval; HR, haard ratio; ITT, intent-to-treat.

For the subgroup of patients that were previously treated with a sunitinib-containing regimen, there were 131 deaths (67.5%) in the axitinib arm and 131 deaths (67.2%) in the sorafenib arm. The HR (axitinib vs sorafenib) was 0.997 (95% CI [0.782, 1.270]) with a 1-sided p-value of 0.4902 (Figure 11).

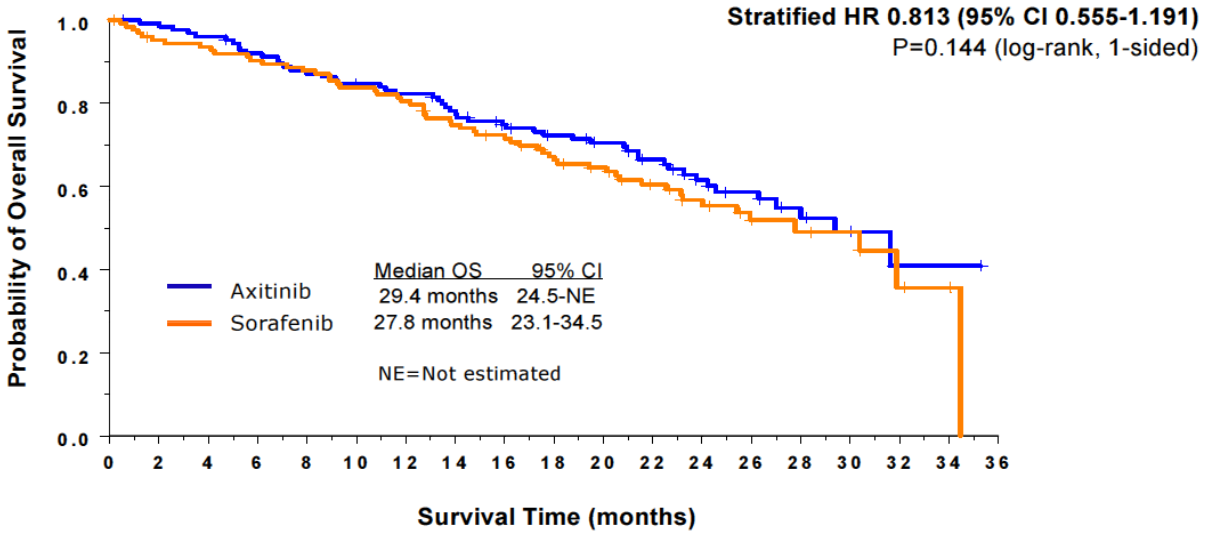
Figure 11: Kaplan-Meier curves of overall survival by treatment – sunitinib refractory population



Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

For the subgroup of patients that were previously treated with a cytokine-containing regimen, there were 51 deaths (40.5%) in the axitinib arm and 57 deaths (45.6%) in the sorafenib arm. The HR (axitinib vs sorafenib) was 0.813 (95% CI [0.555, 1.191]) with a 1-sided p-value of 0.1435 (Figure 12).

Figure 12: Kaplan-Meier curves of overall survival by treatment – cytokine refractory population



Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Secondary efficacy outcome: Objective response rate, IRC assessment (ITT population)

Based on the IRC assessment of the overall stratified analysis, 19.4% (95% exact CI [15.4%, 23.9%]) of axitinib treated patients and 9.4% (95% exact CI [6.6%, 12.9%]) of sorafenib treated patients had an overall confirmed ORR (CR and PR). The risk ratio (axitinib vs sorafenib) was 2.056 (95% CI [1.408, 3.003]) with a 1-sided p-value of 0.0001, indicating a higher likelihood of response in the axitinib arm.

Based on the IRC assessment of the sunitinib-refractory subgroup, 11.3% (95% exact CI [7.2%, 16.7%]) of axitinib treated patients and 7.7% (95% exact CI [4.4%, 12.4%]) of sorafenib treated patients had overall confirmed ORR. The risk ratio (axitinib vs sorafenib) was 1.477 (95% CI [0.792, 2.754]) with a 1-sided p-value of 0.1085.

Based on the IRC assessment of the cytokine-refractory subgroup, 32.5% (95% exact CI [24.5%, 41.5%]) of axitinib treated patients and 13.6% (95% exact CI [8.1%, 20.9%]) of sorafenib treated patients had overall confirmed ORR. The risk ratio (axitinib vs sorafenib) was 2.392 (95% CI [1.434, 3.992]) with a 1-sided p-value of 0.0002.

The ORR results based on Investigator assessment were similar to those from the IRC (data not shown).

Secondary efficacy outcome: Duration of response (ITT population)

Based on the IRC assessment of the overall stratified analysis, the DR was 11.0 months (95% CI [7.4, not estimable]) for axitinib treated patients compared with 10.6 months (95% CI [8.8, 11.5]) for sorafenib treated patients. For the sunitinib refractory subgroup, the DR was 11 months (95% CI [5.2, not estimable]) for axitinib treated patients compared with 11.1 months (95% CI [not estimable, not estimable]) for sorafenib treated patients. For the cytokine refractory subgroup, the DR was 11.0 months (95% CI [7.4, not estimable] for axitinib treated patients compared with 10.6 months (95% CI [5.9, 11.5]) for sorafenib treated

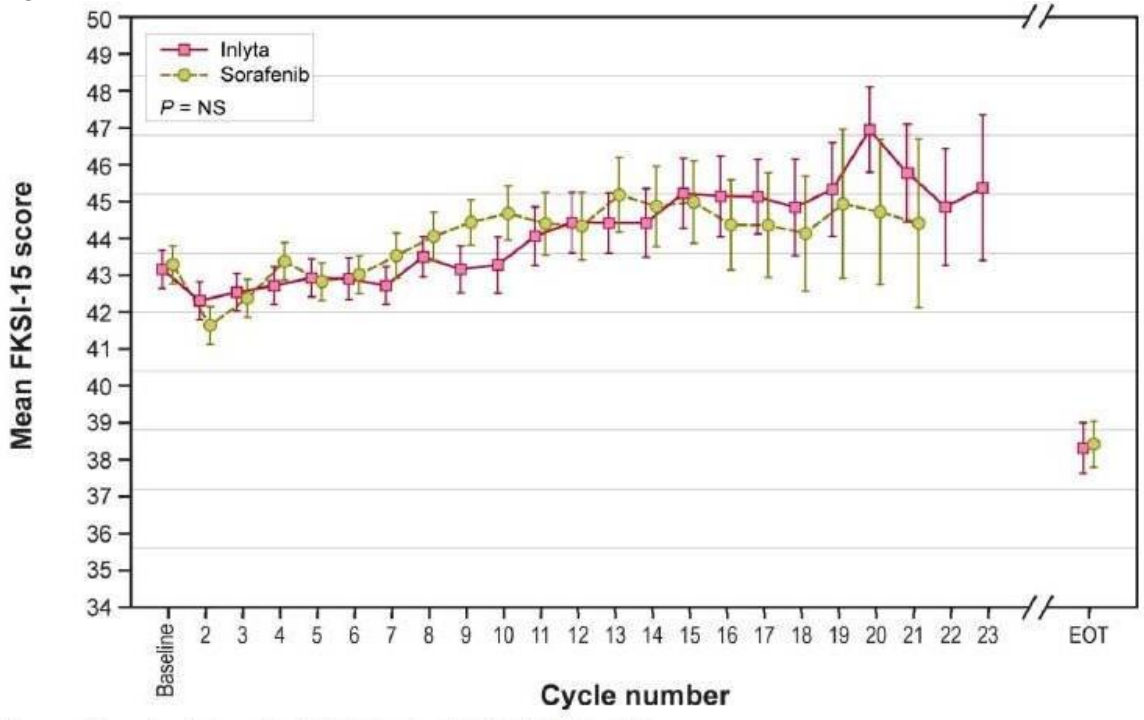
patients. The DR results based on Investigator assessments were similar to those from the IRC (data not shown).

Secondary efficacy outcome: patient reported outcomes (ITT population)

FKSI-15: The 15-item Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) which measures symptoms and QoL in symptoms related to advanced kidney cancer disease including lack of energy, pain, losing weight, bone pain, fatigue, shortness of breath, coughing, bothered by fevers and haematuria. The total FKSI score is the sum of the 15 individual item scores. Higher FKSI scores indicate better QoL.

At baseline, the FKSI-15 questionnaire was completed by 86.4% of patients in the axitinib arm and 85.9% of patients in the sorafenib arm. For all subsequent treatment cycles, completion rates were 90% or higher in both treatment arms. A repeated measures mixed-effects model was used to compare differences between the two treatment arms. There was no significant difference between axitinib and sorafenib post-treatment (p=0.4833) and no significant interaction between treatment and time (p=0.3943). QoL was maintained whilst patients remained on axitinib and sorafenib treatment. At the end of treatment, after patients had progressed, QoL scores were substantially worse, suggesting that patients' QoL is maintained whilst they remain on treatment and free of disease progression.

Figure 13: Observed mean FKSI-15 scores with axitinib and sorafenib



EOT, end of treatment; FKSI, Functional Assessment of Cancer Therapy Kidney Symptom Index.

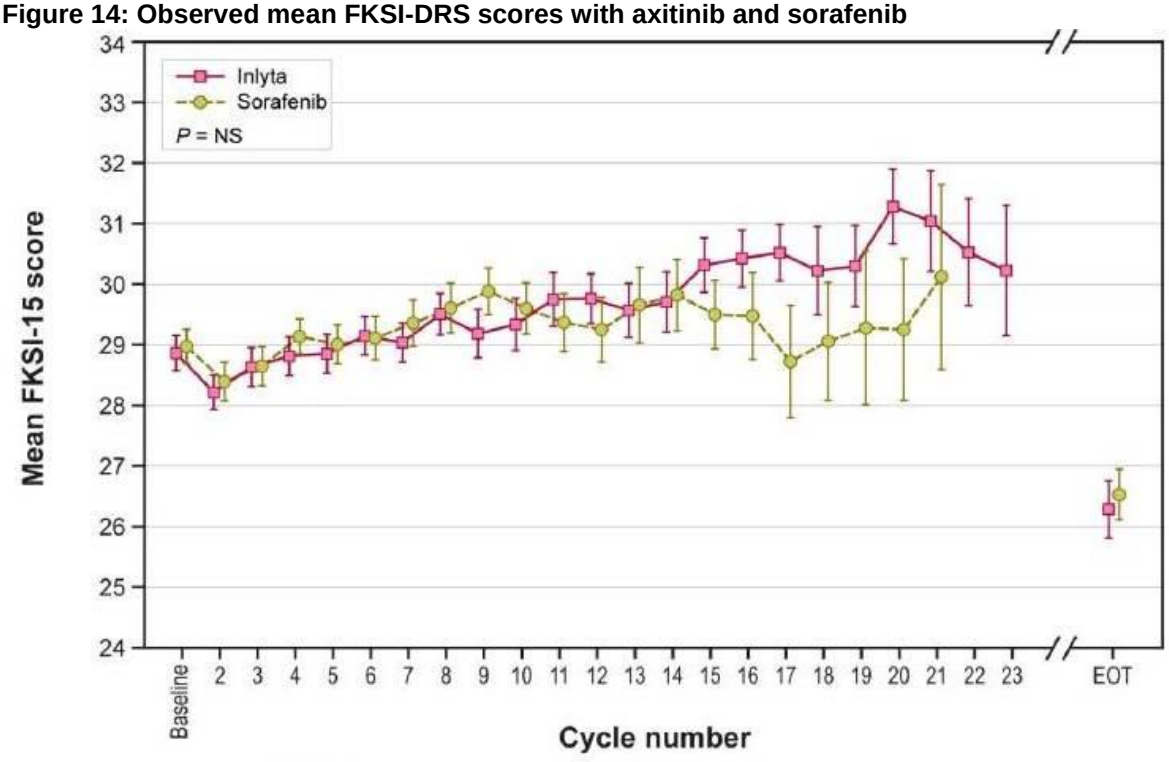
Time to deterioration (TTD) was assessed, where deterioration was defined as the composite endpoint of death or disease progression or a FKSI-15 decrease of ≥ 5 points, whichever occurred first. The results indicate superiority of axitinib over sorafenib, with a HR of 0.829 (95% CI [0.701, 0.981]; 1-sided p-value of 0.0141). The median time to deterioration was 3.1 months for axitinib vs 2.8 months for sorafenib. For the composite

death/progression/deterioration endpoint, there was a 17% risk reduction observed for axitinib vs sorafenib (64).

FKSI-DRS: The total FKSI-DRS specifically measures symptoms related to advanced kidney cancer disease and is the sum of nine individual scores. Higher FKSI scores indicate better QoL.

The results of the FKSI-DRS were similar to those observed with the FSKI-15 questionnaire. A repeated measures mixed-effects model was used to compare differences between treatment arms. The difference between axitinib and sorafenib post-treatment for the FKSI-DRS was 0.12 (95% CI [-0.45, 0.69], p-value=0.6746 (Figure 14). QoL was maintained whilst patients remained on axitinib and sorafenib treatment. At the end of treatment after patients had progressed, QoL scores were substantially worse, suggesting that patients' QoL is maintained whilst they remain on treatment and free of disease progression.

Figure 14: Observed mean FKSI-DRS scores with axitinib and sorafenib



Abbreviations: EOT, end of treatmentFKSI, Functional Assessment of Cancer Therapy Kidney Symptom Index.

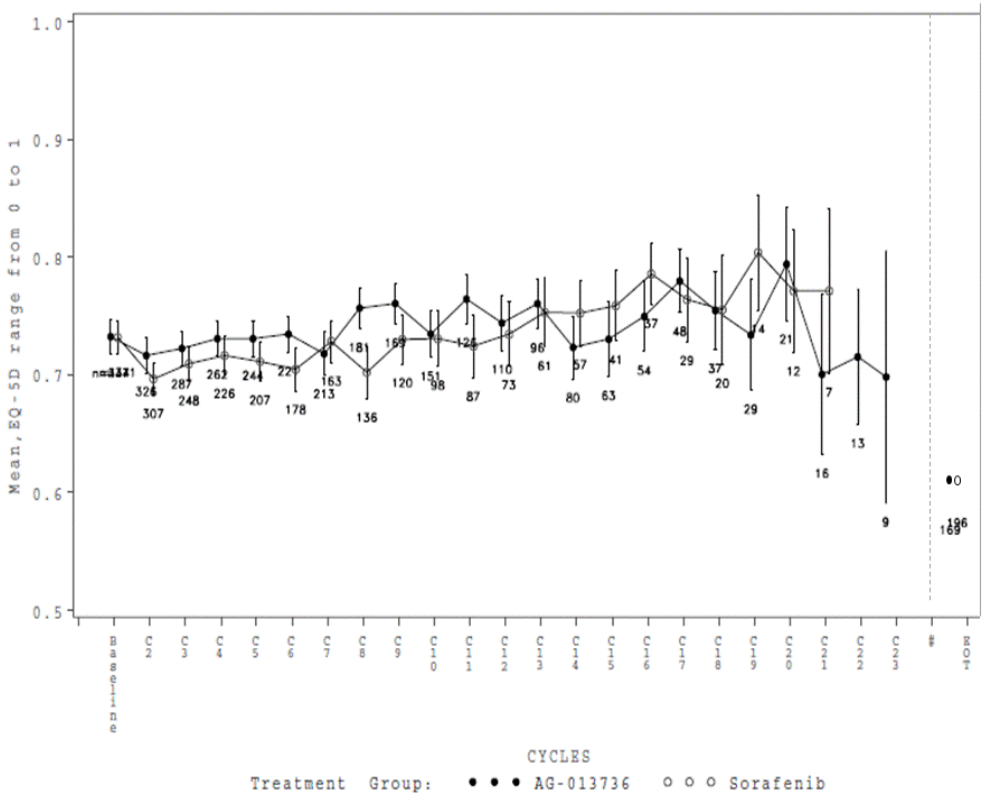
The Kaplan Meier estimate of median TTD in health status (defined as a composite measure of the time between date of randomisation and the date of death, tumour progression, or a decrease of >3 points on the FKSI-DRS, whichever occurred first) was 3.7 months for axitinib and 2.9 months for sorafenib with a HR of 0.838, 95% CI (0.707, 0.993), and p-value of 0.0203. Patients who received axitinib demonstrated a 16% reduction in risk of disease symptom–related deterioration compared with those who received sorafenib (64).

EQ-5D: The EQ-5D consists of five domains of functional impairment: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Low scores represent a higher level of dysfunction.

At baseline, 96.1% of patients in the axitinib arm and 96.1% of patients in the sorafenib arm completed all items of the EQ-5D. A repeated measures mixed-effects model was used to

compare differences between treatment arms; the overall between-treatment comparison for axitinib vs sorafenib was not statistically significant. QoL was maintained whilst patients remained on treatment (i.e. progression free), and declined when patients stopped study medication (mainly due to progression) (Figure 15).

Figure 15: Observed mean EQ-5D scores with axitinib and sorafenib



Note: AG013736 = axitinib

Summary

The AXIS study met the primary endpoint, demonstrating statistically significant improvement in PFS as determined by the IRC (p<0.0001). A statistically significant improvement was also seen in the sunitinib refractory subgroup (p=0.0107) and the cytokine refractory subgroup (p<0.0001). There was a significantly higher ORR in the axitinib arm compared with the sorafenib arm (p=0.0001), however, there was no significant difference in OS between the two treatment groups. In addition, HRQoL was maintained in both treatment arms while patients remained on-treatment and progression free. As axtinib provides a greater PFS benefit, this enables axitinib treated patients to maintain their HRQoL for longer compared with sorafenib treated patients.

6.6 Meta-analysis

6.6.1 *The following steps should be used as a minimum when presenting a meta-analysis.*

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**

- **Statistically combine (pool) the results for the both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

A direct meta-analysis was not possible because only one RCT for axitinib in the population relevant to the decision problem is available.

6.6.2 ***If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.***

N/A

6.6.3 ***If any of the relevant RCTs listed in response to Section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.***

N/A

6.7 Indirect and mixed treatment comparisons

Comparison with best supportive care

- Studies identified in the systematic review of RCTs were assessed for their suitability for inclusion into an indirect comparison of axitinib vs BSC (in line with the NICE scope) in the sunitinb-refractory and cytokine refractory patient populations
- Four relevant trials were identified:
  - AXIS (axitinib vs sorafenib; described in detail in Section 6.3 onwards)
  - TARGET (sorafenib vs placebo)
  - VEG105192 (pazopanib vs placebo)
  - RECORD-1 (everolimus vs placebo).
- The link between axitinib and BSC was provided by the TARGET trial, which compared the efficacy of sorafenib with placebo (used as a proxy for BSC). As the TARGET trial contained patients that had received first-line cytokine therapy only, the only comparison that could be made with sufficient methodological rigour was between axitinib and BSC in the cytokine refractory subgroup
- VEG105192 and RECORD-1 were excluded from the indirect comparison as they did not provide a link between axitinib and placebo and therefore do not provide any additional data of relevance to the decision problem
- A systematic review was conducted to identify studies in which patients received first-line sunitinib treatment followed by BSC after they experienced disease progression in order to identify a link between axitinib and BSC for the sunitinib-refractory subgroup
  - No relevant HRs were identified
  - Two UK studies reported median OS of 4.1 and 4.3 months, respectively for a cohort of patients that progressed on sunitinib
- A simulated treatment comparison (STC) was conducted to create an “adjusted” indirect comparison between the axitinib sunitinib-refractory population from AXIS and the placebo prior-sunitinib population from RECORD-1
- To supplement this analysis, OS hazard ratios from observational data for patients that received BSC or sorafenib following prior-sunitinib therapy were used in an indirect comparison to generate HRs for axitinib vs BSC in a sunitinib-refractory population

Cytokine refractory patients

Indirect comparison

- For the PFS outcome, the HR for axitinib vs placebo in a cytokine refractory population was 0.251 (95% CrI 0.165-0.379), indicating that an axitinib treated patient has approximately a 75% reduction in the hazard of progression compared with placebo
- For the OS endpoint when the comparison was performed with the ITT population that were censored for cross-over in the TARGET trial, the HR was 0.63 (CrI 0.41-0.99),

indicating a 37% reduction in the hazard of death compared with placebo

Sunitinib refractory patients

Simulated treatment comparison

- In order to achieve a comparison of axitinib efficacy vs BSC in patients that received first-line sunitinib therapy, a simulated treatment comparison (STC) was performed to estimate how sunitinib-refractory patients from the AXIS trial would have performed if they had been treated with placebo, using data from RECORD-1
- Using the ITT RECORD-1 placebo cohort:
  - For PFS using the ITT RECORD-1 placebo cohort, the estimated median PFS was 6.9 weeks (1.6 months) for axitinib-like patients if they had received placebo
  - For OS using the ITT RECORD-1 placebo cohort adjust for cross-over using the RPSFT method, the estimated median OS was 36 weeks (8.3 months) for axitinib-like patients assuming that they received placebo

Indirect comparison using observational data

- To support the results of the STC, a post-hoc analysis of real-world data from a Swedish patient registry (RENCOMP) was performed:
  - Overall survival was compared amongst patients that had received first-line sunitinib followed by sorafenib or BSC and estimated HRs were used in an indirect comparison to generate a hazard ratio for axitinib vs BSC in patients that had received prior-sunitinib
  - The estimated OS HR for axitinib vs BSC was 0.619 (95% CI 0.384-0.997).

6.7.1 ***Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.4, appendix 4.***

Please see Section 6.1 for the methods used to identify RCT evidence for axitinib and comparator therapies in the treatment of patients with advanced/mRCC who failed prior systemic therapy. Eligibility criteria and a flow diagram of included and excluded studies can be found in Section 6.2.

6.7.2 ***Please follow the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in Section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.***

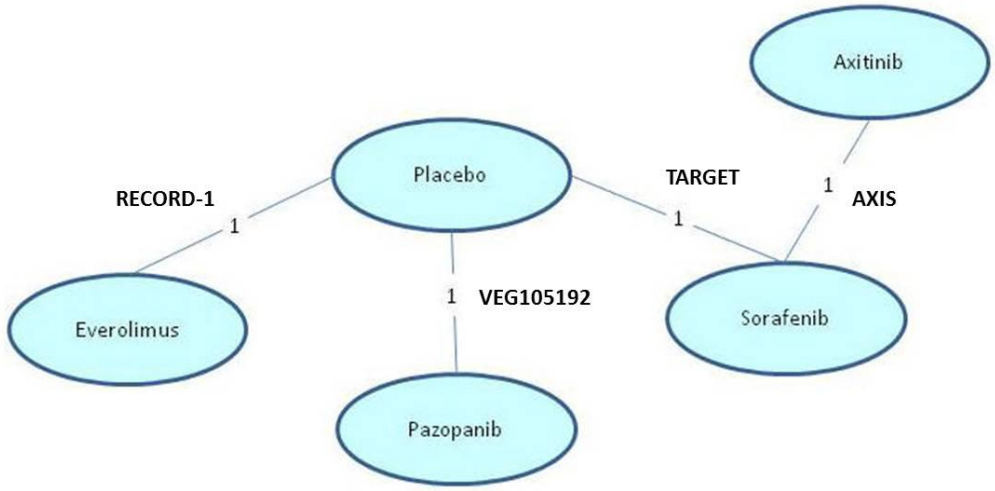
Study selection

Of the publications that were identified (reporting on 25 RCTs, including axitinib studies), seven reported HRs for OS and/or PFS. Of these, two were excluded due to duplication of results and one was excluded as it considered bevacizumab as a monotherapy (outside its

marketing authorisation). One study (pazopanib vs placebo) did not contain mature OS data (at the time of the final PFS analysis, only 61% of the total number of deaths required to perform the final OS analysis had occurred) but was included for the PFS endpoint only. Therefore, four studies were considered for inclusion in the indirect comparison (Figure 16):

- AXIS: a Phase III study of axitinib vs sorafenib (the pivotal trial for axitinib, reported in detail in Section 6.3 and onwards) (51)
- TARGET: a Phase III study of sorafenib vs placebo (79)
- RECORD-1: a Phase III study of everolimus vs placebo (81)
- VEG105192: a Phase III study of pazopanib vs placebo (82) (Used for PFS endpoint only).

Figure 16: Network of studies considered for inclusion in the indirect comparison



Consideration of identified studies for inclusion in the indirect comparison

As can be observed in the network diagram, the TARGET trial was the only study identified that compared sorafenib with placebo, allowing an indirect comparison of axitinib (from the AXIS trial) with placebo (used as a proxy for BSC). The VEG105192 and RECORD-1 trials were excluded as they did not provide a link between axitinib and placebo and therefore do not provide any additional data of relevance to the decision problem in the indirect comparison framework. However, as the RECORD-1 trial was the only study apart from AXIS that reported data on patients that received BSC following sunitinib treatment, this trial was utilised in a subsequent analysis (see Section 6.7.11). An indirect comparison would have required using the TARGET trial (which contained a cytokine-pre-treated population only) to compare axitinib with placebo and therefore may have produced biased results when aiming to compare axitinib with placebo in the sunitinib-refractory population. In addition, the overall survival will be confounded due to crossover in the TARGET study.

The limitations of the evidence network for the indirect comparison are described in further detail below.

Limitations of the evidence network

Any indirect comparison between axitinib and BSC depends on two key pieces of evidence:

1. Relative efficacy of axitinib compared to sorafenib (from the AXIS trial)
2. Relative efficacy of sorafenib compared to BSC (from published Phase III RCTs)

However, there are a number of key shortcomings in both sections of the evidence network which impacted the indirect comparison between axitinib and BSC.

Relative efficacy of axitinib compared with sorafenib (AXIS trial)

As discussed in Section 6.3.2, the study design and reporting of the AXIS trial can be viewed as an unbiased estimate of the relative efficacy in PFS of axitinib vs sorafenib. However, despite a statistically significant improvement in PFS, a similar improvement was not observed in OS. More specifically, there are several reasons which can obscure the true OS benefit with axitinib in the AXIS study.

While many earlier advanced/mRCC trials were able to use placebo comparisons (15, 29, 34), patients now receive multiple lines of treatment. This makes it increasingly difficult to ethically justify placebo-controlled studies in metastatic cancers such as advanced/mRCC where treatments are available and particularly where the majority of patients are likely to progress and die rapidly in the absence of treatment.

The use of an active comparator in an oncology trial setting has several potential benefits and is typically considered a higher hurdle. It allows for direct efficacy evidence which, when a relevant comparison is chosen, can improve the usefulness of the results of the study and their applicability to clinical practice. As discussed in Section 6.10, the use of sorafenib as an active comparator was in line with clinical practice and the standard of care when the AXIS trial was designed and initiated. However, despite the potential of greater external validity, the use of an active comparator means that the incremental PFS benefit a new treatment can demonstrate versus the active comparator will be reduced compared to a placebo comparator. As was demonstrated by Broglio and Berry (83), a smaller incremental PFS difference in a trial increases the number of patients required and the duration of follow-up to show a positive OS trend, and increases the likelihood that random variation in sampling will mask the benefit. The AXIS trial was powered to show a statistically significant difference in PFS in the ITT population and would require a substantially higher statistical power to show a significant OS benefit in the ITT population and even higher in the subgroup populations.

An additional simulation exercise carried out to support the axitinib EMA registration further illustrates this issue. In a sample of 10,000 simulations using the framework described by Broglio and Berry (83) and assumptions similar to the AXIS study ITT population, (i.e. a 2 month PFS benefit over a baseline 4.7 month median, 723 patients, 12.1 months median survival post progression, and a similar censoring pattern), the simulation indicated that an HR of greater than 0.9 was observed over 60% of the time even when the HR was 0.67 for PFS. Thus, in an active-comparison trial like AXIS, where incremental PFS benefit will be less than a placebo-controlled trial, there is a high likelihood that, despite significant PFS superiority, OS benefit may not be convincingly shown. This problem is amplified when considering the cytokine refractory and sunitinib refractory subgroups, as patient numbers (and in the case of the sunitinib refractory subgroup, incremental PFS) are further reduced.

Proving OS may be very costly due to the need for large sample sizes and extended study timeframes when patients are receiving multiple lines of treatment, especially in the case of active comparator studies. This may delay patient access to effective drugs for several years (84, 85).

Difficulty of demonstrating incremental OS benefit in advanced/mRCC

As mentioned above despite having met its primary endpoint of significantly extending PFS in a purely second-line population of advanced/mRCC patients in the ITT and both subgroups, the AXIS study failed to show a statistically significant benefit in OS. Although this presents a drawback from the point of cost-effectiveness analysis, this issue is not limited to the AXIS study. While multiple phase III registration trials in advanced/mRCC have not shown a statistically significant increase in survival with the exception of temsirolimus in poor risk patients, patients are clearly living longer with targeted therapy compared with the immunotherapy era (15, 34). More specifically, median OS is now higher than 2 years with these agents, which represents a significant advance compared with a median OS of 10 to 13 months in the immunotherapy era (32, 86). In addition to advanced/mRCC, many other tumour types have displayed this trend towards positive PFS advantages with little to no subsequent OS gains.

Confounding due to long duration of Survival Post Progression

A potential feature of advanced/mRCC which may impact on the likelihood of demonstrating an OS benefit is the relatively long survival post-progression (SPP) period exhibited by patients in advanced/mRCC trials. This issue is explored in a simulation study carried out by Broglio and Berry (2009) which compared PFS with OS, taking into account the length of time that patients remained alive following disease progression (83). In this analysis, OS was expressed as the sum of PFS and survival post progression (SPP). The authors concluded that for trials with a PFS benefit, lack of statistical significance in OS does not necessarily imply lack of OS benefit, especially where there is a long SPP (e.g., >12 months), since the variability in SPP dilutes the OS comparison and statistical significance is lost; this reflects the situation for advanced/mRCC.

The lack of statistical significance in OS can be explained by patient heterogeneity which is particularly apparent for advanced/mRCC (87) and variability in treatment decisions made after disease progression which dilute the OS differences between treatment arms. In addition, the longer the SPP of patients and the higher the likelihood of receiving subsequent therapy and the more treatment options are available (either approved or in clinical trials) the more difficult it will be to obtain a clear sense of OS benefit (Hotte et al., 2011; Lebwohl et al., 2009).

As patients in the axitinib pivotal trial remained alive for approximately a year after disease progression was documented, this may have had an impact on the OS analysis. Thus, while the AXIS study has not demonstrated an incremental OS benefit over sorafenib, evidence indicates that this is a common feature for advanced/mRCC and not likely a shortcoming of the individual treatment.

Effect of post-study treatment

As mentioned above, an additional key source of OS confounding in the AXIS trial is the use of subsequent treatments after progression. Patients in both treatment arms had access to a number of other approved active therapies after discontinuing their randomized treatment.

As subsequent treatments in the AXIS study were assigned at investigator discretion in a non-randomised manner, OS can effectively be viewed as a non-randomized endpoint subject to substantial confounding.

Subsequent treatments may dilute an OS advantage. Patients who discontinued treatment on this study may have received subsequent therapy based on the judgment of the treating physician.

In the cytokine-refractory subgroup, 46.4% of patients in both the axitinib arm and in the sorafenib arm received subsequent treatment. In addition, 22.7% of patients in the axitinib arm and 20.0% of patients in the sorafenib arm received more than 1 subsequent treatment. In the sunitinib-refractory subgroup, 65.2% of patients in the sorafenib arm and 60.0% of patients in the axitinib arm received subsequent treatment. Additionally, 28.6% of patients in the axitinib arm and 33.2% of patients in the sorafenib arm received more than 1 subsequent treatment. (63). As a consequence, OS will not capture the effect of a specific treatment but sequences of treatment. The longer the SPP of patients and the higher the likelihood of receiving subsequent therapy and the more treatment options there are available (either approved or in clinical trials) the more difficult it will be to obtain a clear sense of axitinib's OS benefit (Hotte et al., 2011; Lebwohl et al., 2009).

Previous NICE appraisals for advanced/mRCC have consistently highlighted the view of both clinical specialists and NICE appraisal committees than an increase in PFS would be expected to result in an increase in overall survival. NICE has agreed that it was appropriate to adjust the OS data to control for confounding using statistical modelling techniques (34, 76). Certain methodological approaches have been examined to adjust for confounding by subsequent therapy (88, 89). However, as they attempt to correct for bias in a patient's likelihood to receive subsequent treatment based on observed covariates, these approaches are data intensive and rely upon a full set of patient characteristics to be recorded at each point of therapy assignment. In practice, due to the limitations of data collection in late-stage metastatic cancer patients, such data were not available in the AXIS study.

In conclusion, the AXIS study can be considered an unbiased representation of the relative efficacy of axitinib compared to sorafenib on PFS. However, the relative efficacy on OS is likely an underestimation. This can be explained due to the difficulty of demonstrating incremental OS in advanced/mRCC, limitations in active comparator studies in the Oncology context, confounding due to post-study treatment, and confounding due to survival post-progression. Thus, it is likely that the current evidence available underestimates the true incremental OS benefit of axitinib.

Limitations of the evidence network: Relative efficacy of sorafenib vs BSC

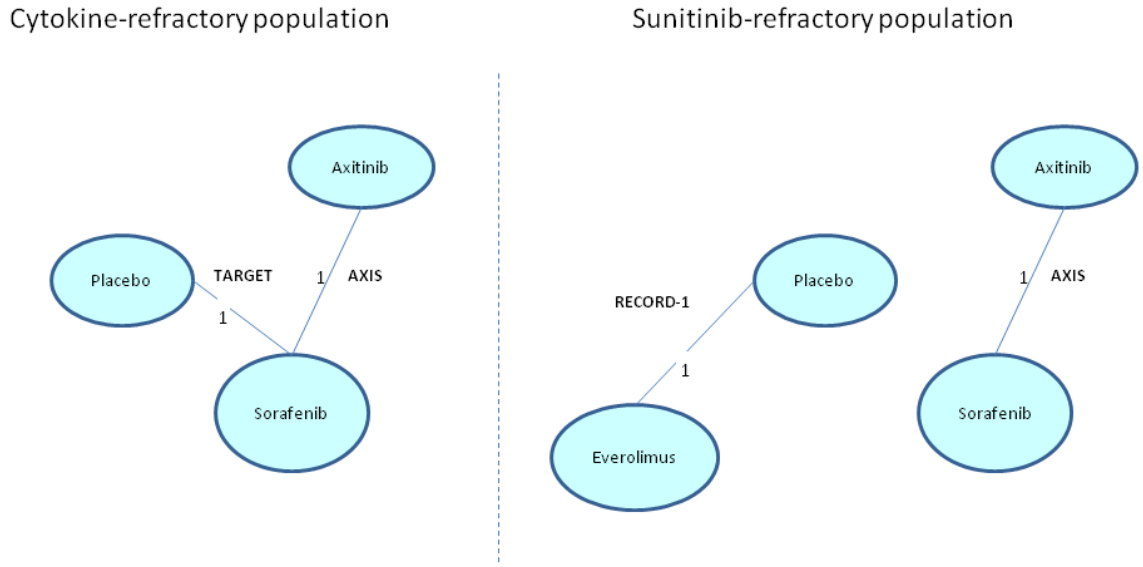
The second component of the evidence network required to make an axitinib to BSC indirect comparison is clinical data demonstrating the relative efficacy of sorafenib compared to BSC in terms of PFS and OS. A robust comparison would require the presence of RCTs in the network which provides incremental PFS and OS data between sorafenib in BSC in both the cytokine refractory and sunitinib refractory subgroup. However, this data is again subject to limitations. Specifically:

1. Lack of sorafenib versus BSC clinical data in a sunitinib refractory population
2. Confounding in OS data due to crossover in the TARGET study

Lack of sorafenib vs BSC evidence in the sunitinib refractory population

As previously described, many clinicians consider a cytokine refractory, TKI naive population to comprise a markedly different subgroup of patients compared with a sunitinib refractory population. Given the lack of comparability between these sub-populations, it was necessary to examine the evidence network comparing axitinib and BSC separately in the cytokine refractory and sunitinib refractory populations. The network diagrams for these two populations are presented in Figure 17.

Figure 17 Evidence networks for the cytokine-refractory and sunitinib refractory populations.



As the network diagrams in Figure 17 indicate, while there is RCT evidence comparing sorafenib versus BSC in a prior cytokine subgroup (provided by the TARGET trial), no such evidence is available for the prior sunitinib subgroup. The TARGET trial enrolled patients that had received prior-cytokine therapy and did not include patients that had received prior-VEGF inhibitors as when the trial was designed, no VEGF inhibitors had received marketing authorisation. There was therefore heterogeneity compared with the population enrolled into the AXIS trial, where the majority of patients received either first-line sunitinib or first-line cytokine treatment.while there is RCT evidence comparing sorafenib versus BSC in a cytokine refractory subgroup (provided by the TARGET trial), no such evidence is available for the sunitinib refractory subgroup. The TARGET trial enrolled patients that had received prior-cytokine therapy and did not include patients that had received prior-VEGF inhibitors. There was therefore heterogeneity compared with the population enrolled into the AXIS trial, where the majority of patients received either first-line sunitinib or first-line cytokine treatment.

Due to this heterogeneity, it was only possible to perform an indirect comparison between axitinib and BSC in the the cytokine refractory population, usig the the AXIS and TARGET trials. An indirect comparison of the sunitinib-refractory population via the TARGET study would assume that a sunintib refractory and cytokine refractory population are interchangeable. This assumption is implausible as clinicians including UK clinical experts consider a cytokine refractory population whom are TKI naïve to comprise a different subgroup of patients compared with a TKI refractory population. The cytokine refractory patients may have failed more rapidly (90) than a population refractory to TKIs in the first-line

setting and therefore may be an easier population to treat with a TKI in a second-line setting as indicated by the higher median PFS. OS and tumour response achieved by the cytokine refractory population in the AXIS study versus the sunitinib-refractory population. As no other studies were identified that investigated the efficacy of sorafenib vs placebo, it was not possible to perform an indirect comparison of the sunitinib refractory subgroup from the AXIS trial and placebo.

Confounding due to crossover in the TARGET study

In contrast to the sunitinib refractory population, where no direct evidence was available to make the linkage between axitinib and BSC, the cytokine refractory population included one RCT (TARGET) comparing BSC and sorafenib. For PFS, both the AXIS and TARGET studies included progression via RECIST-defined PFS in a cytokine refractory population as their primary outcome measure. Neither treatment effect was confounded. Thus the estimated HR for PFS with the indirect comparison of axitinib vs BSC in the cytokine refractory population can be viewed as appropriate.

However, for OS, the TARGET treatment effect was substantially confounded by crossover from the control to treatment arm at the point of progression. While the TARGET trial publication includes a HR which censors those patients who cross over, this approach can lead to severe selection bias if patient's probability of switching treatments is strongly related to their underlying prognosis, which is likely in this setting as patients often switch treatments because their condition has deteriorated. A recent study carried out by UK health economists including members of the NICE Decision Support Unit (91) which examined different methods for correcting for crossover concluded that this methodology potentially underestimates the true measurement of incremental OS benefit in both simulated and RCT datasets. As the TARGET study data has never been analysed with a more appropriate methodology for dealing with treatment switching in randomised clinical trials (such as a Rank Preserving Structural Failure Time Model, a NICE-validated methodology for correcting for crossover (78)), the overall survival benefit of sorafenib vs. BSC in the TARGET study is uncertain and potentially biased. As previous examples demonstrate, rank preserving structural failutre time (RPSFT) can be expected to substantially improve the hazard ratio in a trial where crossover is present in favour of active treatment. In the case of the NICE appraisal for everolimus in advanced/mRCC, the original non-significant hazard ratio of 0.87 (95% CI 0.65 to 1.17) resulted in an adjusted RPSFT hazard ratio of 0.53 (92). In the case of sunitinib in gastrointestinal stromal tumour (GIST), the application of RPSFT analysis reduced the initial OS hazard ratio of 0.876 (95% CI 0.679 to 1.129,) to 0.505 (95% CI 0.262 to 1.134). Given the proportionately similar hazard ratio from the TARGET study (0.88, 95% CI 0.74–1.04), it is possible that the application of RPSFT analysis to the TARGET study data would produce a similar result.

Methods to overcome the limitations in the evidence network

Systematic review of sunitinib progression

In order to identify a link between axitinib and BSC for the sunitinib-refractory subgroup, an additional systematic review was performed to identify studies in which patients received first-line sunitinib treatment followed by BSC after they experienced disease progression. The aim was to identify hazard ratios for survival in patients that had received sunitinib

treatment followed by BSC, in order to conduct an indirect comparison with sunitinib-refractory patients from the AXIS trial.

Simulated treatment comparison

Simulated treatment comparisons (STCs) (93) is a novel technique to derive indirect comparisons between competing treatments (say A and B). Unlike mixed treatment comparisons (MTCs) which provide an average measure of the difference between A and B across all studies, STCs aim to answer a more specific question: what difference could we expect if A and B had been compared in the same trial.

STCs rely on individual patient data (IPD) for the treatment from an index trial (e.g., one used as the basis of a submission), and summary data (usually published reports) for the competitor from one or more studies. The studies for the treatment being compared must be generally compatible in terms of the type of population included, measurement methods, timeframe of observation, reporting of information, etc. The studies are not required to be exactly identical in these dimensions, but there must be sufficient overlap so that findings from one study can be assumed to be applicable in the setting of the other trial.

Even with close compatibility between the studies, it is unlikely that the characteristics of the patients will be identical, so that comparisons of outcomes between the trials may be confounded by these differences. STCs are specifically designed to adjust for these differences. This is done by using the index trial data to build a predictive equation for each endpoint for which a comparison is desired. We can denote this equation in a general way as having the following form:

$$\mu = X\beta$$

where μ represents some parameterization of the outcome variable. For instance, if the outcome of interest is a time-to-event variable like PFS or OS, μ would be the scale parameter in a parametric survival model; X represents a vector of predictors of the outcome and β represents the corresponding coefficients. We note that X may include an indicator for study group, and correspondingly, β would include a treatment effect coefficient. In some applications, the equation may be built from a single (e.g., experimental) treatment; in oncology trials, this may be done when outcomes in the reference arm is biased due to crossover, for example. For the explanations that follow, it is assumed that the equation is built from the primary treatment arm (i.e., A in the current notation).

The STC then proceeds with following steps:

1. If the comparator treatment (B) had been included in the index trial the equation would have included a term for a comparison of A vs. B, as follows:

   $$\mu = X\beta + \delta_{B \text{ vs. } A} Z_{B \text{ vs. } A}$$

   where δ is a coefficient representing the effect of B compared to A (e.g., expressed as a log hazard ratio), and Z is an indicator of treatment group.

2. Since the index trial provides no information on treatment B, external data from published sources must be used to estimate δ. For time-to-event outcomes like PFS or OS, this information may be in the form of a Kaplan-Meier curve or specific percentiles of the time-to-event distribution, like the median.

3. δ can then be estimated by calibrating the equation to the target values in step 2; that is, finding a value that will yield a predicted outcome that equal the target values (e.g., median survival) established in step 2. To account for the fact that this target value reflects outcomes in the population for treatment B, the predictions must be adjusted to the profile of the comparator's study.

   This is done by setting X to the mean characteristics of the population in study B:

   $$\mu_B = X_B\beta + \delta_{B \text{ vs. } A} Z_{B \text{ vs. } A}$$

   This represents outcomes for patients like those in the competitor study, had they received treatment A (since $X\beta$ predicts outcomes for treatment A). Thus, the difference between predictions based on $X_B\beta$ (e.g., the median time) and the target value (e.g., median time observed in study B) reflects the difference in the effects of treatment A and B.

4. The value of δ is then a function of this difference in outcome measures. This may be calculated algebraically in situations where the target values are simple numeric values (e.g., medians). When the target is a distribution (e.g., Kaplan-Meier curve), a grid search may be performed to identify the value that minimizes differences between the prediction and target values.

Similar methodologies have been accepted in recent HTA appraisals to overcome gaps in the evidence network which rule out a standard indirect comparison approach, including NICE TA171 (Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy) (94) and the SMC approval of everolimus in pancreatic neuroendocrine tumour (95).

The systematic review carried out to support this submission (reported in Section 6.1) identified only one RCT reporting BSC efficacy in a TKI refractory advanced/mRCC patient population: the RECORD-1 trial, of everolimus versus best supportive care. Patients in the RECORD-1 trial were required to have received prior treatment with a TKI, making it a more comparable population to the AXIS sunitinib refractory population. While crossover to active treatment at progression was allowed in RECORD-1, a validated methodology (RPSFT) was applied to correct for the impact of crossover on the OS estimate. Additionally, as this RPSFT analysis was reviewed and corrected by the ERG group during the everolimus NICE appraisal, this analysis can be viewed as an independently validated, crossover-adjusted estimate of BSC survival after a previous TKI.

Despite some similarities between RECORD-1 and AXIS in terms of requiring at least one prior treatment, there are several differences between the two trials which could potentially confound the comparison. First, in contrast to AXIS, where all patients included in the study were required to have progressed on first-line therapy by RECIST-defined criteria, in the overall RECORD-1 population, 14% of patients (n=58) discontinued previous TKI therapy because of unacceptable toxicity. Among the subgroup of 58 patients who were intolerant to previous TKI therapy, 45 patients and 13 patients were randomly assigned to everolimus and placebo, respectively. Thus, patients in the RECORD-1 study could have discontinued prior treatment due to intolerance and therefore results would be more reflective of a first-line study.

Secondly, only 43 patients in the everolimus arm of RECORD-1 had sunitinib as there only previous therapy (i.e. purely second-line) in comparison with 194 patients in the AXIS trial.

Of the 43 sunitinib refractory patients in RECORD-1, it was not known how many patients entered the trial due to sunitinib intolerance (96). The inclusion of patients who were sunitinib intolerant rather than refractory would potentially bias the results in favour of the RECORD-1 patients; those patients who discontinue treatment due to intolerance can be considered to be analogous to first-line patients and would be expected to respond better to treatment compared with patients who failed first-line treatment.

Thirdly, in contrast to the AXIS study, where patients were required to have received only one prior therapy (sunitinib or a cytokine, or bevacuzimab + interferon-α or temsirolimus), patients in the RECORD-1 study were allowed to have received more than one previous therapy and could have been treated with sunitinib or sorafenib, as well as a cytokine in some cases (see Section 6.7.2).

The differences in previous therapies between AXIS and RECORD-1 are a source of uncertainty when comparing the two trials using the STC framework. The impact of this difference is difficult to determine and could potentially bias the comparison in several ways. For example, if a patient receives multiple lines of therapy it could potentially indicate a better response to treatment or a more slowly progressing course of disease, and thus a better prognosis and higher expected survival for RECORD-1 patients compared to AXIS. However, this could also indicate increased likelihood of resistance or lack of response to previous therapies in patients who had several lines of treatment and therefore a lower expected survival and less likelihood of benefitting from additional lines of treatment. As the prognostic MSKCC scores of patients in the RECORD-1 study were more favourable than those in AXIS at the start of the study (15% of BSC patients had poor MSKCC score in RECORD-1 vs. 33% sunitinib refractory patients receiving axitinib in AXIS), it is possible that the former is more relevant. Of note, the impact of the differences in prior therapies on survival between the two trials may in part be accounted for by the adjustment for differences in MSKCC scores in the STC analysis.

The second source of confounding between AXIS and RECORD-1 is the inclusion of patients in the RECORD-1 study whom discontinued previous TKI therapy due to intolerance. While intolerance to first-line therapy was not an inclusion criterion in the AXIS study, the inclusion of these patients in the RECORD-1 could potentially introduce a prognostic bias in favour of RECORD-1 as patients who discontinued due to intolerance may have less progressed disease and a higher expected survival in their subsequent treatment. This is further supported by a subgroup analysis which showed that the subgroup of intolerant patients in RECORD-1 had a higher PFS than the overall study population (96).

Thus, the inclusion of these patients in RECORD-1 would be expected to overestimate the survival of patients in favour of RECORD-1 compared to AXIS, and thus result in a more conservative incremental efficacy estimate of axitinib versus BSC.

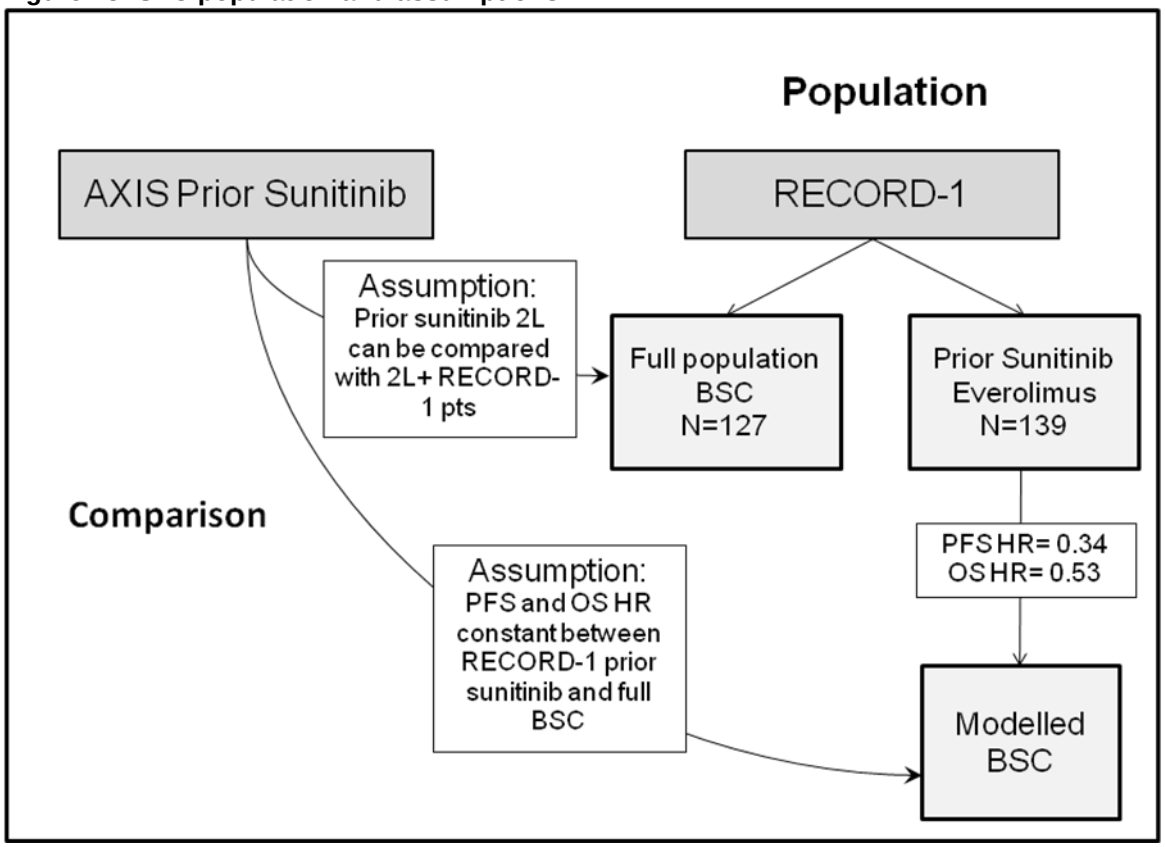
Another consideration in comparing the two studies is that RECORD-1 study patients were allowed to have received previous treatment with sorafenib as well as sunitinib. When attempting to compare the axitinib sunitinib-refractory arm from AXIS with the BSC prior sunitinib sub-population from RECORD 1, the ideal RECORD-1 population for comparison would have consisted of those patients in the BSC arm that had progressed on sunitinib after receiving only one line of therapy. However, while an exploratory analysis of a small subgroup of prior sunitinib only patients (n = 56) in the RECORD-1 has reported a median PFS of 4.6 months with everolimus (n = 43) and 1.8 months with placebo (n = 13) (HR, 0.22;

95% CI, 0.09–0.55; P < .001), the median OS and patient characteristics have never been reported for this population. The closest available patient populations reporting overall survival data to allow the STC comparison were the ITT BSC population (corrected for crossover using the RPSFT method) and patients receiving everolimus treatment with only prior sunitinib therapy. In the ITT population, median PFS was 4.9 months with everolimus and 1.9 months with BSC and median OS was 14.8 months with everolimus and 14.4 months with placebo.

Given the shortcomings of the available evidence, two approaches were examined in the STC to make the BSC comparison. The first was to compare the axitinib sunitinib-refractory population from AXIS with the ITT BSC (RPSFT-adjusted) treatment arm from RECORD-1 (76, 97). This approach assumes that the RECORD-1 ITT BSC population has similar median OS and patient characteristics to the RECORD-1 prior sunitinib population. The second approach was to compare with the everolimus prior sunitinib population (reported by Di Lorenzo et al (98)) and then apply the RPSFT-adjusted hazard ratio for everolimus to BSC to create a modelled prior sunitinib BSC arm. This approach does not make the assumption of equivalent patient characteristics and median OS between the prior sunitinib and ITT BSC population in RECORD-1, but it does assume an equivalent incremental efficacy for everolimus versus BSC between the prior sunitinib and ITT population. Because neither of these assumptions could be independently verified, both approaches were examined in modelling scenarios.

Figure 18 graphically displays the two approaches used to create the STC comparison, and the assumptions necessary for each approach.

Figure 18: STC population and assumptions



Abbreviations: BSC, best supportive care; HR, hazard ratio; OS, overall survival; 2L, second line; PFS, progression-free survival.

Database analysis

Due to the lack of published work reporting on the survival of patients that progressed on first-line sunitinib treatment and then received BSC, a retrospective analysis of sunitinib-refractory patients from a Swedish database (Renal Comparison; RENCOMP) containing data from three registries (The Swedish Cancer register, The National Patient Register and The Swedish Prescribed Drug Register) was carried out to determine the OS of patients who received sunitinib first-line, followed by BSC or sorafenib second-line.

The aim of this comparison was to estimate the OS hazard ratio between patients who received sunitinib followed by sorafenib and sunitinib followed by BSC. These estimated hazard ratios using RENCOMP were then included in an indirect comparison alongside the AXIS sunitinib refractory hazard ratio between axitinib and sorafenib to generate indirect hazard ratios between axitinib and BSC in a sunitinib refractory population.

Indirect comparison methodology

Table 13 presents a summary of the methodology of the studies used in the indirect comparison and Table 14 details the inclusion and exclusion criteria for each study.

Table 13: Summary of methodology of RCTs used in the indirect comparison

	AXIS	TARGET
Study references	Rini et al 2011 (51) CSR (46) and supplemental CSR with final OS data (63)	Escudier et al, 2007 (79) and Escudier et al, 2009 (80) for final OS data
Intervention and comparator	Axitinib (N=361) 5 mg BD starting dose Sorafenib (N=362) 400 mg BD starting dose	Sorafenib (N=451) 400 mg BD Placebo (N=452) BD
Population	Patients with mRCC following failure of a prior systemic first-line regimen containing one of the following: sunitinib, bevacizumab + IFNα, temsirolimus or cytokine(s).	Patients with metastatic clear cell RCC who had progressed after one prior systemic therapy in the previous 8 months
Design	Randomised, multicentre, international Phase III study. Cross-over was not permitted.	Randomised, double-blind, placebo-controlled, Phase III study. Cross-over was allowed following the first PFS analysis.
Duration of study	Treatment was to continue until disease progression, intolerable adverse drug reactions or withdrawal of consent.	Until disease progression or withdrawal due to AEs.
Method of randomisation	Patients were randomised in a 1:1 ratio to receive either axitinib 5 mg BD or sorafenib 400 mg BD through a centralised registration and randomisation system (IVRS) using a permuted block design of size 4. Patients were stratified according to ECOG PS (0 or 1) and previous treatment regimen.	Patients were stratified according to country and MSKCC prognostic score (favourable or intermediate) and randomly assigned to study groups in a 1:1 ratio with a block size of 4.
Method of blinding	Open-label, however the independent assessment of the primary endpoint (PFS) was done in a blinded manner by the IRC	Double-blind
Location	175 sites in 22 countries	117 centres in 19 countries
Tumour assessments	CT/MRI and bone scans were performed at screening, at 6 weeks and 12 weeks, then every 8 weeks thereafter.	Progression of disease was determined by CT or MRI, clinical progression or death by RECIST. Assessments of responses required confirmatory findings on CT or MRI 4 or more weeks after the initial determination of a response.
Primary outcome	PFS assessed by the IRC	OS
Secondary outcomes	PFS (Investigator assessed), OS, ORR, duration of response, HRQoL, TTD, safety	PFS, ORR, AEs, HRQoL

	AXIS	TARGET
Duration of follow-up	Patients were followed until disease progression, intolerable adverse drug reactions or withdrawal of consent.	Until disease progression or withdrawal due to AEs, until death.

Abbreviations: AE, adverse event; BD, twice daily; CR, complete response; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IRC, independent review committee; IVRS, interactive voice response system; mRCC, metastatic renal cell carcinoma; MRI, magnetic resonance imaging; MSKCC, Memorial Sloan-Kettering Cancer Centre; OD, once daily; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response, RECIST, response evaluation criteria in solid tumours; TTD, time to deterioration.

Table 14: Inclusion/exclusion criteria of studies used in the indirect comparison

	AXIS	TARGET
Inclusion criteria	• ≥ 18 years • Histologically/ cytologically confirmed mRCC with a clear cell subtype component • Evidence of measurable disease (by RECIST) • Progressive disease criteria per RECIST (Version 1.0) after 1 prior systemic first-line regimen for mRCC. The prior regimen had to have contained 1 of the following: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s) • ECOG performance status of 0 or 1 • Life expectancy of ≥ 12 weeks • At least 2 weeks since the end of prior systemic treatment (4 weeks for bevacizumab + IFNα) • Adequate renal, hepatic and haematological function	• ≥ 18 years • Histologically confirmed metastatic clear cell RCC which had progressed after 1 systemic treatment • ECOG PS ≤ 1 • MSKCC favourable or intermediate risk • Life expectancy of ≥ 12 weeks • Adequate bone marrow, liver, pancreatic and renal function • Prothrombin time of or partial thromboplastin time <1.5 x ULN
Exclusion criteria	• Prior treatment of mRCC with more than 1 systemic first-line regimen • History of malignancy other than RCC • A need for CYP3A4 inhibiting/inducing or CYP1A2 inducing drugs • CNS metastases • Uncontrolled hypertension • Myocardial infarction, uncontrolled angina, congestive heart failure or cerebrovascular accident in previous 12 months • DVT or pulmonary embolism in previous 6 months	• Brain metastases • Previous exposure to VEGF inhibitors

Abbreviations: BP, blood pressure; CNS, central nervous system; DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group performance status; IFNα, interferon-alpha; mmHg, millimetres of mercury; ms, milliseconds; mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Centre; NYHA, New York Heart Association; RECIST, response evaluation criteria in solid tumours; RCC, renal cell carcinoma; ULN, upper limit of normal; VEGF, vascular endothelial growth factor.

Baseline characteristics

Baseline characteristics of patients in the trials used in the indirect comparison are presented in Table 15. Between the two trials, patients were similar in terms of age and gender distribution. In addition, at least 91% in each trial had received prior nephrectomy.

There were differences between the trials in the reporting of metastatic sites. The TARGET trial only reported liver and lung metastases, whilst AXIS reported a broader list of metastatic sites. In both studies, 70-80% of patients had lung metastases at baseline and 26-39% had liver metastases. In the TARGET trial, the majority of patients had a favourable MSKCC risk score and there were no patients enrolled with a poor score. In the AXIS trial, the baseline population was split evenly between favourable, intermediate and poor risk scores.

There were substantial differences between the trials with regards to patients' prior treatment regimen:

- In AXIS (51), patients received sunitinib, cytokines (IL-2 or IFNα), bevacizumab + IFN-α, or temsirolimus as first-line therapy
- In TARGET (79), 80% of patients received cytokines (IL-2 or IFNα); patients who received VEGF treatments were not included as no VEGF treatments were licensed at the time of the trial.

However due to a lack of alternative sources of evidence for placebo/BSC and comparator treatments, both studies described above were used in the analysis. In addition, the TARGET trial was essential for the indirect comparison as it was the only study identified that investigated the relative efficacy of sorafenib (the only common comparator with the AXIS trial) with placebo.

Table 15: Patient characteristics in RCTs used for the indirect comparison

	AXIS		TARGET	
	Axitinib N=361	**Sorafenib N=362**	**Sorafenib N=451**	**Placebo N=452**
Age, median (range)	61 (20-82)	61 (22-80)	58 (19-86)	59 (29-84)
Male, n (%)	265 (73)	258 (71)	315 (70)	340 (75)
ECOG performance status, n (%)				
0	195 (54)	200 (55)	219 (49)	210 (46)
1	162 (45)	160 (44)	223 (49)	236 (52)
>1	1 (<1)	0	7 (2)	4 (1)
Missing data	0	0	2 (<1)	2 (<1)
MSKCC risk score, n (%)				
Favourable	100 (28)	101 (28)	233 (52)	228 (50)
Intermediate	134 (37)	130 (36)	218 (48)	223 (49)
Poor	118 (33)	120 (33)	0	0
Missing data	9 (2)	11 (3)	0	1 (<1)
Previous nephrectomy, n (%)	327 (91)	331 (91)	422 (94)	421 (93)
Previous systemic therapy, n (%)	361 (100)	362 (100)		
Sunitinib	194 (54)	195 (54)		
Cytokines	126 (35)	125 (35)	374 (83)	368 (81)
Bevacizumab	29 (8)	30 (8)		
Temsirolimus	12 (3)	12 (3)		
Common metastatic sites				
Lung	274 (75.9)	292 (80.7)	348 (77)	348 (77)
Liver	102 (28.3)	103 (28.5)	116 (26)	117 (26)
Bone	119 (33.0)	107 (29.6)	NR	NR
Lymph node	209 (57.9)	202 (55.8)	NR	NR
Other	139 (38.5)	130 (35.9)	NR	NR
Kidney	81 (22.4)	77 (21.3)	NR	NR

	AXIS		TARGET	
	Axitinib N=361	**Sorafenib N=362**	**Sorafenib N=451**	**Placebo N=452**
Brain	NR	NR	NR	NR
Pleural effusion	18 (5.0)	18 (5.0)	NR	NR
Ascites	2 (0.6)	5 (1.4)	NR	NR

Abbreviations: ECOG, Eastern cooperative oncology group; MSKCC, Memorial Sloan-Kettering Cancer Centre; NR, not reported.

Critical appraisal of relevant RCTs

A critical appraisal of the RCTs used in the indirect comparison is provided in Section 10.5 (Appendix 5).

Results of relevant RCTs

The results of the RCTs that were used in the indirect comparison are summarised in Table 16. The outcomes used in the indirect comparison have been presented – PFS as assessed by the IRC and OS.

Table 16: Results of relevant RCTs

	AXIS	TARGET
Median PFS, IRC assessed	***ITT population:*** Axitinib (6.7 months) vs sorafenib (4.7 months) HR: 0.665 (95%CI [0.544-0.812]) p<0.0001 ***Sunitinib-refractory population:*** Axitinib (4.8 months) vs sorafenib (3.4 months) HR: 0.741 (95% CI [0.573-0.958] p=0.0107 ***Cytokine-refractory population:*** Axitinib (12.1 months) vs sorafenib (6.5 months) HR: 0.464 (95% CI [0.318-0.676]) p<0.0001	***ITT population:*** Sorafenib (5.5 months) vs placebo (2.8 months) HR: 0.44 (95% CI [0.35-0.55]) p<0.001
Median OS	***ITT population:*** Axitinib (20.1 months) vs sorafenib (19.2 months) HR: 0.969 (95% CI [0.800-1.174]) p=0.3744 ***Sunitinib-refractory population:*** Axitinib (15.2 months) vs sorafenib (16.5 months) HR: 0.997 (95% CI [0.782-1.270]) p=0.4902 ***Cytokine-refractory population:*** Axitinib (29.4 months) vs sorafenib (27.8 months) HR: 0.813 (95% CI [0.555-1.191]) p=0.1435	***ITT population:*** Sorafenib (17.8 months) vs placebo (15.2 months) HR: 0.88 (95% CI [0.74-1.04]) p=0.146 ***Censored for cross-over:*** Sorafenib (17.8 months) vs placebo (14.3 months) HR: 0.78 (95% CI [0.62-0.97]) p=0.029

Abbreviations: CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival

6.7.3 *Provide a summary of the trials used to conduct the indirect comparison.*

A summary of the two trials used to conduct the indirect comparison is provided in Table 16. A network diagram is presented in Figure 19.

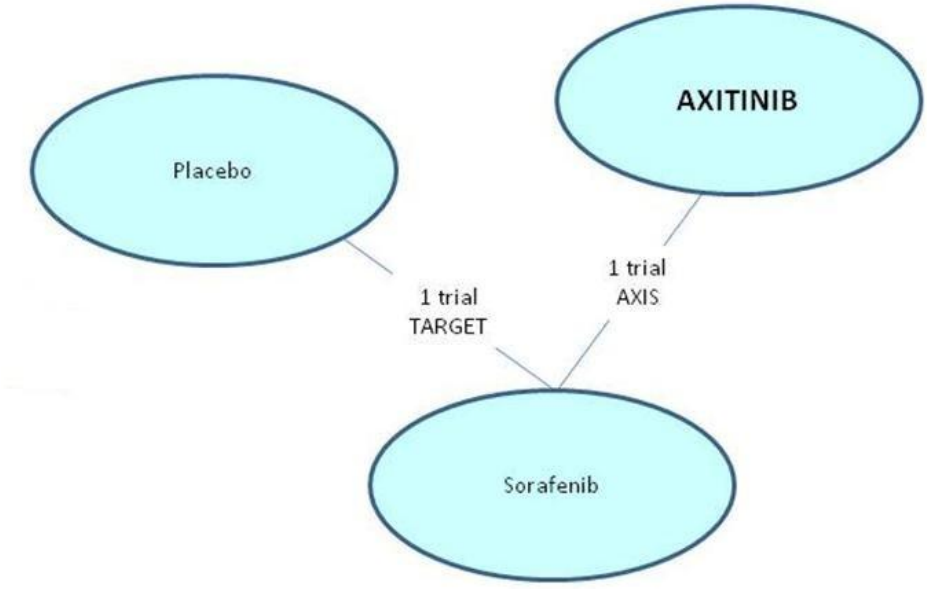
.

Table 16: Summary of the trials used to conduct the indirect comparison

No. trials	References of trials	Intervention (Axitinib)	Comparator B (Sorafenib)	Comparator C (BSC)
1	AXIS	√	√	
1	TARGET		√	√

Abbreviations: BSC, best supportive care.

Figure 19: Network diagram for the indirect comparison



6.7.4 *For the selected trials, provide a summary of the data used in the analysis.*

HRs were used for this analysis rather than time to progression (TTP) which is dependent on arbitrary cut-offs and could bias the results.

The hazard ratios provided in Table 17 were used from the AXIS and TARGET trials.

Table 17: Input data

	AXIS (axitinib vs sorafenib)	TARGET (sorafenib vs placebo)
	HR (95% CI)	
PFS (IRC)	***Cytokine refractory population:*** 0.464 (0.318-0.676)	***ITT population:*** 0.44 (0.35-0.55)
OS	***Cytokine refractory population:*** 0.813 (0.555-1.191)	***ITT population censored for cross-over:*** 0.78 (0.62-0.97)

Abbreviations: CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.

6.7.5 *Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.*

The indirect comparison was performed using Bayesian Markov Chain Monte-Carlo sampling to determine the relative efficacy of the treatments. Sampling was performed using WinBUGS. A fixed effects model was used due to the limited availability of relevant data for use in the model. In this case because hazard ratios entered to the model and not individual treatment effects, the approach assumes that the relative treatment effect (i.e. HR) for one treatment pair is the same across all trials. Since there was only one trial per pairwise HR, this assumption was appropriate in this analysis. Non-informative prior distributions were used. A non-informative prior assumes that all possible The WinBUGS code for the fixed-effects model is provided in Section 10.14 (Appendix 14).

Point estimates of the HR for each pair of treatments along with 95% credible intervals (CrI) were calculated from 5,000 simulated draws from the posterior distribution after a burn-in of 20,000 iterations.

6.7.6 *Please present the results of the analysis.*

The results of the indirect comparison are presented for the cytokine refractory populations for the endpoints of PFS and OS. PFS and OS were chosen as the endpoints for the indirect comparison as they were the key outcome measures in the axitinib clinical trial programme.

Progression free survival: cytokine refractory subgroup

The results of the indirect comparison in the cytokine refractory subgroup are presented in Table 18. A HR of 0.251 for the treatment comparison axitinib vs placebo corresponds to a 75% reduction in the hazard of progression with axitinib compared with placebo (used as a proxy for BSC).

Table 18: PFS – cytokine refractory subgroup

Treatment comparison	Median HR	95% CrI
Axitinib vs placebo	0.251	0.165-0.379
Axitinib vs sorafenib	0.464	0.318-0.676

Abbreviations: CrI, credible interval; HR, hazard ratio; PFS, progression-free survival.

Overall survival: cytokine refractory subgroup

As patients in the TARGET trial were allowed to cross-over to sorafenib treatment from the placebo group at the first PFS analysis, this could have influenced the overall survival of the patients. Therefore, axitinib was compared with placebo through the overall ITT population and the population censored for crossover from the TARGET trial.

The results of the OS analysis are presented in Table 19. A hazard ratio of 0.63 for axitinib vs placebo in the ITT population censored for cross-over means that an axitinib treated patient has a 37% reduction in the hazard of death compared with placebo (Table 19).

Table 19: Overall survival – cytokine refractory subgroup

TARGET population	Treatment comparison	Median HR	95% CrI
ITT censored for cross-over	Axitinib vs placebo	0.63	0.41-0.99
	Axitinib vs sorafenib	0.81	0.56-1.19

Abbreviations: CrI, credible interval; HR, hazard ratio, ITT, intent-to-treat.

Conclusion

Limited RCT data were available for the indirect comparison of axitinib with BSC in the treatment of patients that had received first-line sunitinib or cytokine treatment.

The systematic review identified one RCT which compared the efficacy of sorafenib vs placebo in a second-line patient population (TARGET). In this study, 80% of patients received prior cytokine treatment. Patients were excluded from enrolling if they had received previous VEGF inhibitors. The TARGET trial therefore provided a comparison for the cytokine refractory population from the AXIS trial for the PFS endpoint, but precluded an appropriate comparison with the sunitinib-refractory population, due to the differences in the treatments that patients received first-line.

For the PFS endpoint, the hazard ratio for axitinib vs placebo was 0.251, suggesting that an axitinib treated patient has approximately a 75% lower hazard of progressing compared with someone in the placebo group.

For the OS endpoint, a hazard ratio of 0.63 for axitinib vs placebo in the ITT population censored for cross-over was reported, but there was no difference in OS between axitinib and placebo when compared with the overall ITT population from the AXIS trial.

As it was not possible to perform a robust comparison for the sunitinib-refractory population in the AXIS trial due to a lack of RCT data, further statistical analyses were required.

6.7.7 *Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.*

The variable used to describe the heterogeneity between trials in Bayesian analysis is τ^2. The square root of this is the estimated standard deviation of underlying effects across the studies. Because the data for each pairwise treatment comparison came from single studies, there was no heterogeneity between trials within the model and therefore no assessment of heterogeneity was undertaken.

6.7.8 *If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.*

As only a single study was available for each of the pair-wise comparisons, excluding trials would have excluded the treatment in question from the analysis.

As described above, there was heterogeneity in the populations that entered the trials in terms of prior treatment received; however it was not possible to exclude TARGET from the analysis as this would have removed the only trial linking axitinib with placebo (BSC).

6.7.9 *Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.*

As described in Section 6.7.7, no assessments of heterogeneity were performed as there was only a single study available for each pair-wise comparison. A network-meta analysis could not be performed due to a lack of trials that linked between different treatments and therefore no testing of inconsistency was possible.

6.7.10 *A systematic review to identify clinical studies (RCTs and non-RCTs) reporting efficacy and safety data in patients with advanced/mRCC who received BSC following progression with first-line sunitinib treatment.*

In order to identify a link between axitinib and BSC for the sunitinib-refractory subgroup, an additional systematic review was performed to identify studies in which patients received first-line sunitinib treatment followed by BSC after they had experienced disease progression. The aim was to assess the survival in patients that had received sunitinib treatment followed by BSC and potentially identify hazard ratios between sorafenib and BSC, in order to conduct an indirect comparison with sunitinib-refractory patients from the AXIS trial. The search strategy and inclusion criteria for this systematic review are presented in Section 10.15 (Appendix 15).

The systematic review identified several full text papers that investigated the effects of sunitinib prior to nephrectomy, however these publications were not considered relevant as use of sunitinib in this setting is unlicensed and currently under investigation. In total, four studies were identified; three conference abstracts and one poster presentation. As none of the studies identified full published papers, there were limited data available for extraction. A summary of the results from the studies identified is presented in Table 20.

Miscoria et al (31) reported on survival after progression of patients that continued sunitinib treatment following progression of disease compared with patients who discontinued sunitinib treatment. They noted that survival after progression was longer for patients that continued to receive sunitinib after progression because of consistent clinical benefit compared with patients that discontinued sunitinib treatment upon progression, an observation which they attributed to a remaining residual effect of sunitinib. Median survival for all patients was 4.1 months (95% CI: 3.2 – 5.9).

A retrospective study of UK patients (30) investigated outcomes of patients who had received sunitinib therapy. Following sunitinib failure, 31% of patients remained on sunitinib treatment despite disease progression. This study reported OS for the whole group (4.3 months [95% CI: 2.2-7.3]) with no reference to OS for patients who discontinued sunitinib treatment following progression. In addition, 40% of patients had also received previous immunotherapy.

An abstract by Albiges et al (99) reported on the prognosis of European patients with rapidly progressive disease following first-line sunitinib treatment. Second-line treatment was administered in 82 (57%) patients: 23 with everolimus, 20 with temsirolimus, 33 with sorafenib, 2 with axitinib, 2 with bevacizumab+sunitinib and 2 with chemotherapy. OS for the whole population, including those patients who received second-line treatment, was 6.97 months following discontinuation from sunitinb treatment.

A retrospective study of Medicare claims in the USA (100) reported on discontinuation and survival in patients with advanced RCC who received sunitinib treatment. The median length of treatment with sunitinib was 4.71 months. In this study, 59% of patients discontinued treatment but the reason was not reported. The median survival for patients that discontinued therapy was 5.2 months.

Table 20: Overview of the reported outcomes of the included studies

Study (Country)	*Reported study outcomes*
Albiges et al., 2011 (99) Europe	**Median OS** • 6.97 months (range, 1-33) • 64% of patients were still alive with a median follow-up of 9 months after sunitinib discontinuation
Liu et al., 2009 (100) USA	**Mean treatment length with sunitinib** • 4.71 months (range, 0.13-25.31) • Rate of drug discontinuation: 59.01% **Median survival following sunitinib discontinuation** Median 5.2 months
Miscoria et al., 2011 (31) UK	**Median survival after progression (SAP), months (95 % CI)** *All patients:* • 4.1 (3.2-5.9) (20% of patients had SAP ≥ 1 year) *In the cohort of the patients (50%) continuing on sunitinib:* • 11.6 (5.6-14.6) **Three independent risk factors associated with improved SAP in a multivariate analysis:** • Duration of sunitinib treatment prior to progression ≥1 year • ECOG PS 0-1 • Only 1 metastatic site **16 patients had the three favourable risk factors:** • 9 patients had a SAP>12 months • 11 had an overall survival of more than 2 years
Poffiri et al., 2010 (30)	**The median time to death after progression on sunitinib, months (95 % CI):**

Study (Country)	*Reported study outcomes*
UK	• 4.3 (2.2-7.3)

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; SAP, survival after progression.

As evidence was required to complete the network for axitinib vs BSC in the sunitinib-refractory population, it was necessary to adopt other approaches in order to provide a robust comparison of the relative efficacy of axitinib vs BSC in a sunitinib-refractory population to inform the economic evaluation. The systematic review did however provide evidence for the poor prognosis of patients who progress following first-line sunitinib treatment, with the two UK studies reporting similar median OS times of 4.1 months and 4.3 months (30, 31).

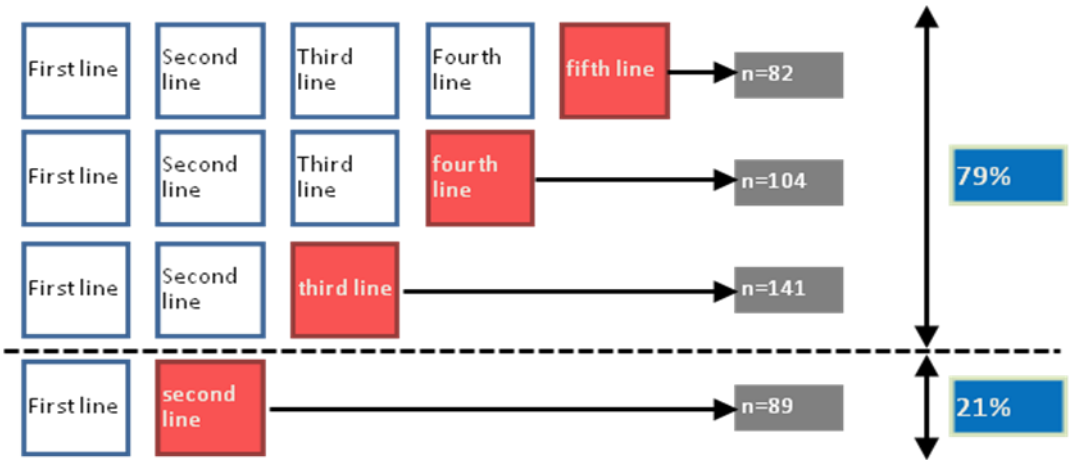
6.7.11 *Simulated treatment comparison*

An STC was performed to compare progression-free survival (PFS) and overall survival (OS) for axitinib vs. everolimus and best standard of care (BSC) based on the AXIS and RECORD-1 trials .

The characteristics of patients who had received prior sunitinib treatment in the AXIS and RECORD-1 trials are presented in Table 21.There were a number of differences between patient characteristics at baseline in the AXIS trial and the RECORD-1 trial, including number of previous treatments received (patients in RECORD-1 could also have received prior cytokine treatment) and MSKCC risk score (more patients in the AXIS trial had a high risk score). Figure 20 displays a visual representation of the extent of previous lines of therapy in RECORD-1. While all patients in the sunitinib-failure population of the AXIS trial had failed exactly one prior line of treatment, 79% of patients in RECORD-1 had received at least two prior systemic therapies and therefore the RECORD-1 trial should not be considered strictly second-line. In addition, patients in RECORD 1 were not required to have progressed on previous lines of therapy and thus may have experienced intolerance as opposed to resistance. In addition, patients in the RECORD-1 trial had higher performance status (as measure by ECOG and Karnofsky performance score) than patients in the AXIS trial.

Please note, baseline patient characteristics were not reported for the prior sunitinib patients that received placebo in RECORD-1, and therefore characteristics for the whole placebo population were utilised.

Figure 20: RECORD-1 – previous lines of therapy



STC methodology

Predictive Equations for PFS and OS:

Patient level data from the AXIS trial were analysed to derive parametric failure-time (survival) equations incorporating baseline predictors of the endpoint. These equations were based on the axitinib arm only. The approach used for estimating parametric survival equations is the same as that used in the economic model and is fully detailed in section 7.3.2. Of the five distributions examined in the full parametric survival analysis, the two best fitting (log-normal and Weibull) were used in the STC.

Identification of potential outcome predictors:

From the AXIS patient level data and prior clinical knowledge, predictive factors were identified that may have been influential on the length of the final PFS or OS. These included sex, age, nephrectomy status, previous radiotherapy, previous cytokine therapy, MSKCC score, clear cell carcinoma, ECOG performance status and time on sunitinib treatment (Table 21).

Selecting the outcome predictors:

Univariate regression analyses were performed to determine which of the factors listed above were predictive of PFS and /or OS. That is, one factor at a time was analysed to determine which resulted in significantly longer/ shorter PFS or OS and these were included in a multivariate equation (one for PFS and one for OS). Characteristics that were identified as being predictive in the univariate analyses (i.e. having a statistically significant coefficient with p-value <0.10) were then considered further. Multivariate analyses incorporated these characteristics simultaneously and the final equations were determined by manually trimming the model to include only significant predictors (p values <0.10).

Validating the equations:

The final equations were checked for validity, i.e. that they aligned with clinical knowledge, and their ability to replicate the source data. These equations formed the basis for the simulation of the “missing arms”.

Target Values for Comparisons of Axitinib vs. Everolimus and BSC

Ideally, the STC would rely on calibration to the full observed Kaplan-Meier survival curve for everolimus and BSC, but these were not reported for the relevant RECORD-1 populations. Therefore, calibration was carried out using the median PFS and OS times. Calibration to the median assumes that everolimus, BSC and axitinib curves for OS and PFS arise from the same type of survival distribution with a common shape.

Since survival estimates for the prior sunitinib placebo only population were not reported for the RECORD-1 study, two data sources were examined for the comparison, each necessitating different assumptions:

ITT RECORD-1 placebo: As the prior sunitinib placebo population was not available, the first approach taken was to compare the AXIS sunitinib refractory patients with the ITT placebo population of RECORD-1. As the RECORD-1 ITT placebo population includes patients that have previously received sunitinib and/or sorafenib, this approach assumes that prior sunitinib patients have equivalent patient characteristics and outcomes to prior sorafenib patients. The median PFS and OS estimates of this patient population are 7.8 weeks (1.8 months), and 43.4 weeks (10.0 months), respectively (97). Due to cross-over in the RECORD-1 trial, median reported OS for BSC group from RPSFT analysis (i.e. 10 months) was used for calibration of the OS curve. However median OS of 10 months was from the RPSFT analyses using the entire BSC cohort and not sunitinib-refractory patients only, therefore the adjustment factor derived from this analysis is likely to be conservative. This is supported by evidence from the RECORD-1 study where prior sunitinib patients receiving everolimus had median OS of 12.6 months (98) compared to 14.8 months in the ITT population.

RECORD-1 prior sunitinib everolimus: The second approach taken was to compare the prior-sunitinib AXIS patients to the prior sunitinib RECORD-1 patients in the everolimus treatment arm (denoted as prior sunitinib everolimus). This population was reported by DiLorenzo et al (98), and achieved median PFS and OS times of 16.9 (3.9 months) and 54.4 weeks (12.6 months), respectively. Median PFS for everolimus patients who failed prior sunitinib was taken from Motzer et.al, 2010 due to results presented in Di Lorenzo contradicting Motzer et al (i.e., 5.6 months vs. 3.9 months median PFS for sunitinib-refractory patients). An attempt was made to follow up with the authors to clarify the discrepancy in these two measurements, however, it is still unclear how the results in the Di Lorenzo study were obtained or why they contradict the previous publication.

Since these patients received everolimus, the survival curves generated by the STC were required to be further adjusted by the application of the PFS and OS hazard ratios from the RECORD-1 study (between everolimus and placebo) to create modelled "AXIS-like" placebo curves. This was done by applying the hazard ratio from the RECORD-1 study to the STC curve after the STC was completed. This approach does not require the assumption of similar characteristics and outcomes between the RECORD-1 prior sunitinib and ITT population. However, as the hazard ratios used to model the everolimus-placebo PFS and OS relationships are from the AXIS ITT population, it does require the assumption of equivalent incremental efficacy for everolimus vs BSC between the prior sunitinib and RECORD-1 ITT population.

As neither one of these assumptions was considered de facto more valid than the other, the STC explored both approaches. Table 21 displays a full breakdown of patient

characteristics and median PFS and OS times for these two patient populations and the AXIS sunitinib refractory population.

Table 21: Patient characteristics – AXIS and RECORD-1

	AXIS (46) ITT sunitinib-refractory axitinib N=194	RECORD-1 (98) Prior sunitinib everolimus N=127	RECORD-1 (97) ITT placebo patients N=139
Male, %	74.2	79.5	76
Age, median (range)	61 (22-82)	59 (28-81)	60 (29-79)
Prior nephrectomy, %	88.1	91.3	N/A
Prior radiotherapy, %	23.2	30.7	N/A
MSKCC risk score, %			
Favourable (0)	19.8	28.1	28
Intermediate (1)	41.4	54.7	57
Poor (≥ 1)	36	17.2	15
Clear cell RCC, %	97.9	100	
ECOG or Karnofsky performance status, %			
ECOG 0/ KPS 90-100	51.6	59.5	68
ECOG 1/ KPS 70-80	48.4	40.5	33
ECOG 2/ KPS 50-60	0	0	0
Missing	0	0.8	0
Weeks on sunitinib, median (range)	41.4 (2.7-471)	41.3 (1.3-120)	N/A
Previous cytokine treatment, %	0	Not known but >0	Not known but >0
Target values used in STC			
Median PFS, weeks	20.8	16.9	7.8
Median OS, weeks	65.9 (15.2 months)	54.4 (12.6 months)	43.4 (10.0 months)

Abbreviations: ECOG, Easter Cooperative Oncology Group; KPS, Karnofsky performance status; MSKCC< Memorial Sloan-Kettering Cancer Centre; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

The calibration of the equations for the STC is described in Section 10.16 (Appendix 16).

Results

Progression-free survival

Predictors of progression-free survival

From the covariates tested, only MSKCC risk categories and age were found to be predictive of PFS (Table 22). As expected, worse prognostic scores at baseline were negatively associated with PFS. Older age was associated with longer PFS. However due to very similar median age in the axitinib and everolimus arms (59 vs. 61 years old), inclusion of the age has minimal impact on the adjustment factor derived from the STC analyses.

Table 22: Predictors of PFS and associated coefficient estimates

Predictors	Lognormal estimate [95% CI]	Weibull estimate [95% CI]
Intercept	0.5455 (-0.3277;1.4186)	0.8065 (-0.0339;1.6468)
MSKCC		
Favourable vs poor/NA	0.8405 (0.4116;1.2695)	0.8575 (0.4352;1.2799)
Intermediate vs poor/NA	0.241 (-0.0928;0.5747)	0.2256 (-0.0896;0.5409)
Age	0.0149 (0.0009;0.0289)	0.0179 (0.0038;0.032)

Abbreviations: CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Centre; N/A, not available; PFS, progression-free survival.

Calibrated PFS for axitinib-like patients - ITT RECORD-1 placebo

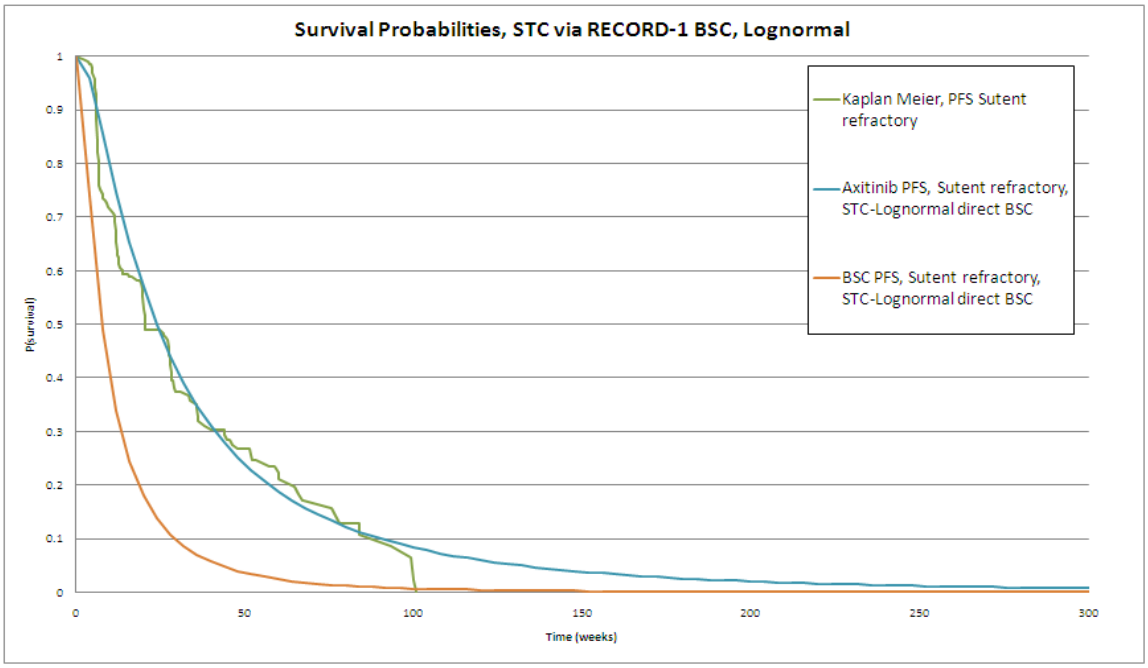
The two distributions identified as best-fitting and incorporated in the STC were lognormal and weibull. Section 7.3.2 describes the methodological approach behind the choice of these distributions.

Lognormal distribution: For PFS via the ITT RECORD-1 placebo cohort, the derived adjustment factor was [redacted], corresponding to a median of 6.9 weeks (1.6 months) for axitinib-like patients if they had received placebo.

Weibull distribution: The derived adjustment factor was [redacted], corresponding to a predicted median of 7.4 weeks (1.7 months).

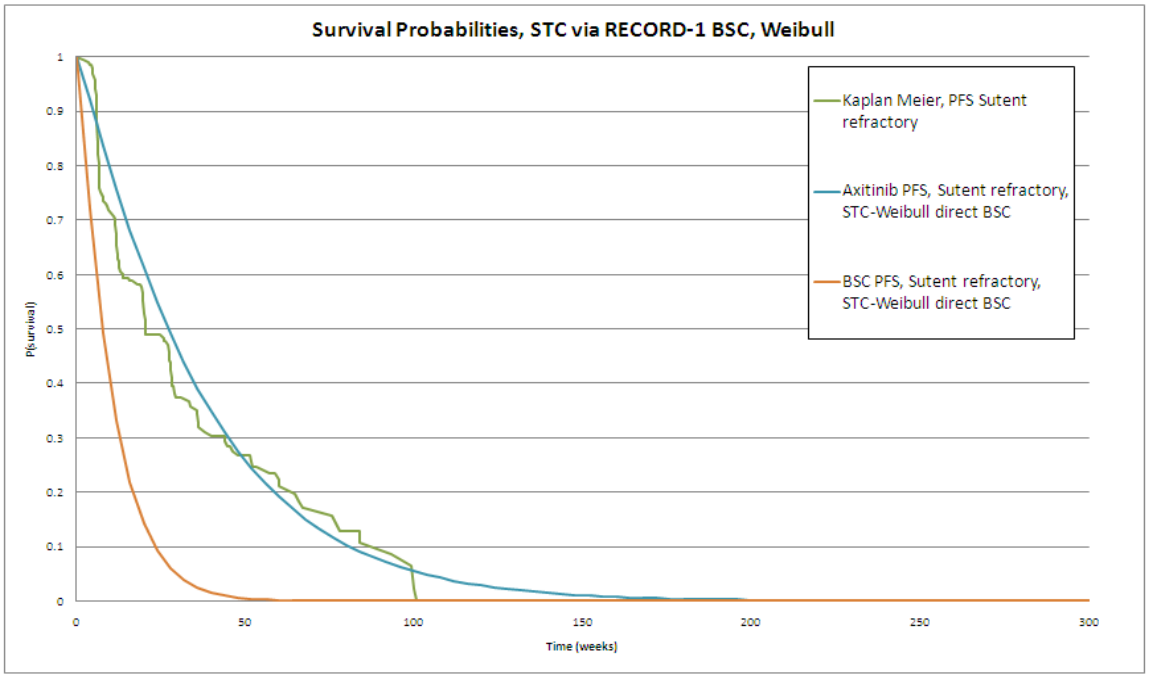
[redacted], respectively. Figure 21 and Figure 22 display the survival probabilities for the lognormal and Weibull curves, respectively.

Figure 21: Lognormal PFS distribution via RECORD-1 ITT placebo population



Abbreviations: BSC, best supportive care; PFS, progression-free survival; STC, simulated treatment comparison.

Figure 22: Weibull PFS distribution via RECORD-1 ITT placebo population



Abbreviations: BSC, best supportive care; PFS, progression-free survival; STC, simulated treatment comparison.

Calibrated PFS for axitinib-like patients - RECORD-1 prior sunitinib everolimus patients

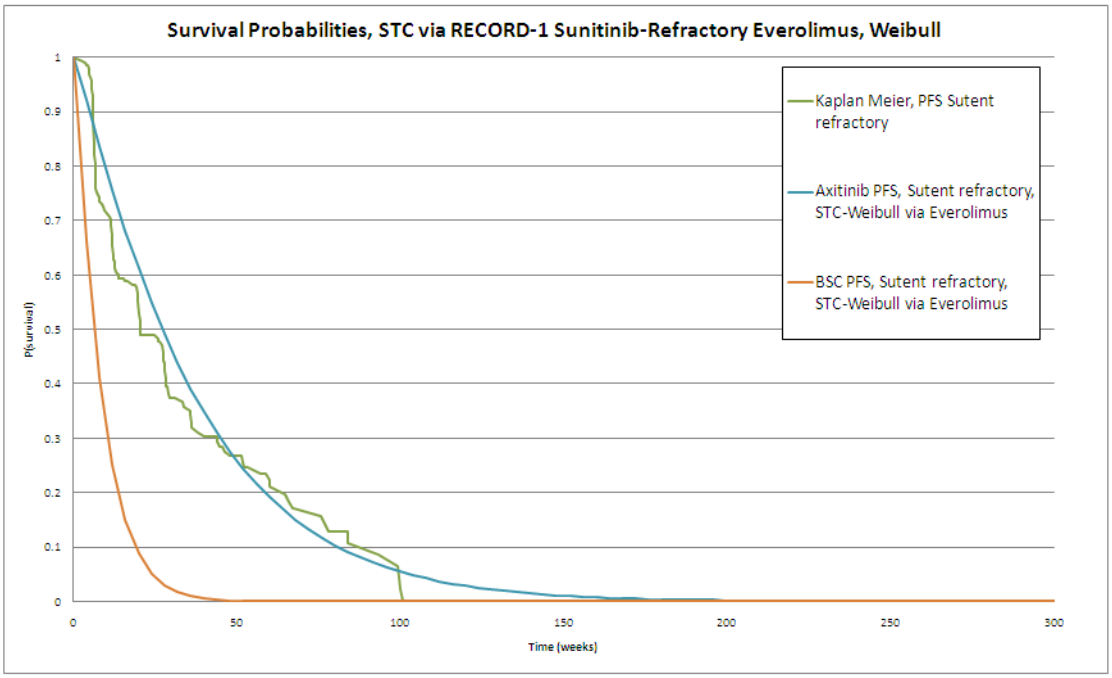
Lognormal distribution: The derived adjustment factor calculated for the RECORD-1 sunitinib-refractory everolimus patients was [redacted], corresponding to a median PFS of 15.6 weeks (3.6 months).

Weibull distribution: Assuming a Weibull distribution, the derived adjustment factor was [redacted], corresponding to a predicted median PFS of 15.7 weeks (3.6 months).

[redacted]

The prior sunitinib PFS hazard ratio from the RECORD-1 study (HR =0.34; 95% CI: 0.23-0.51) was applied to the everolimus STC curve to generate a modelled AXIS-like, prior sunitinib PFS curve. As the lognormal model does not support the application of a hazard ratio, the Weibull was the only option explored in the model. Figure 23 displays the survival probabilities calculated using this approach.

Figure 23: Weibull PFS distribution via RECORD-1 prior sunitinib everolimus + prior sunitinib HR if both treatments had been included in AXIS RCT for sunitinib-refractory patients



Abbreviations: BSC, best supportive care; PFS, progression-free survival; STC, simulated treatment comparison.

A summary of predicted STC survival times for PFS is presented in Table 23.

Table 23: Summary of Predicted (Mean and Median) STC Survival Times: PFS

	Observed median (months)	Predicted median with Weibull (months)	Predicted median with Lognormal (months)	Difference in mean (Weibull / Lognormal)
ITT placebo	1.8	1.6	1.7	[redacted]
Prior sunitinib everolimus	3.9	3.6	3.6	[redacted]

Abbreviations: BSC, best supportive care; TT, intent-to-treat.

Overall survival

Predictors of overall survival

Of the covariates tested, prior duration of sunitinib therapy and baseline MSKCC risk score were found to be predicted of OS (Table 24). The estimated effects associated with prior duration of sunitinib therapy and MSKCC were consistent with expectations: worse performance score at baseline and shorter duration of prior sunitinib therapy were negatively associated with OS. The other parameters investigated were not significant. These characteristics were used to derive a curve with the treatment effect of the comparator arm, and similar patient characteristics to the AXIS sunitinib-refractory population.

Table 24: Predictors of OS and associated coefficient estimates

Predictors	Lognormal estimate [95% CI]	Weibull estimate [95% CI]
Intercept	2.0956 (1.8166;2.3746)	2.625 (2.369;2.8809)
MSKCC		
Favourable vs poor/NA	1.5225 (1.0983;1.9467)	1.3968 (0.9084;1.8851)
Intermediate vs poor/NA	0.5983 (0.2981;0.8985)	0.4929 (0.2183;0.7675)
Duration of prior sunitinib	0.0029 (-0.0005;0.0064)	0.0013 (-0.0021;0.0046)

Abbreviations: CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Centre; N/A, not available; OS, overall survival.

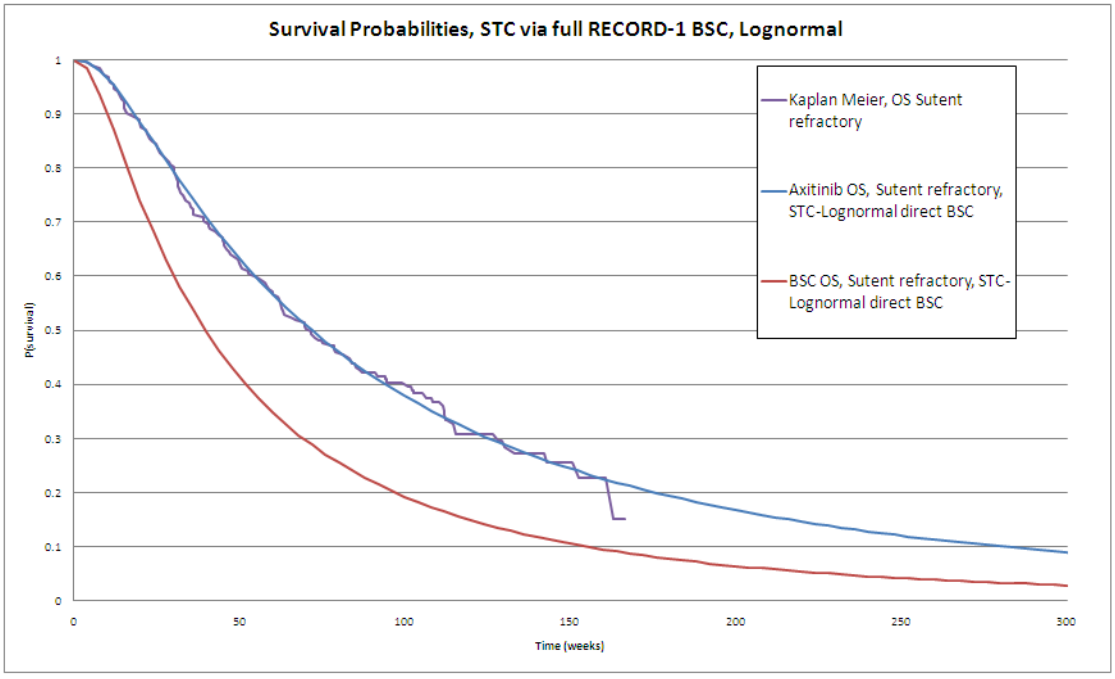
Calibrated OS for axitinib-like patients - ITT RECORD-1 placebo

Lognormal distribution: For the comparison with the RECORD-1 ITT placebo OS cohort, the derived adjustment factor (i.e., treatment effect) was [redacted] corresponding to a median of 36 weeks (8.3 months) for axitinib-like patients assuming that they received placebo.

Weibull distribution: The derived adjustment factor was [redacted], corresponding to a predicted median of 35.6 weeks (8.2 months).

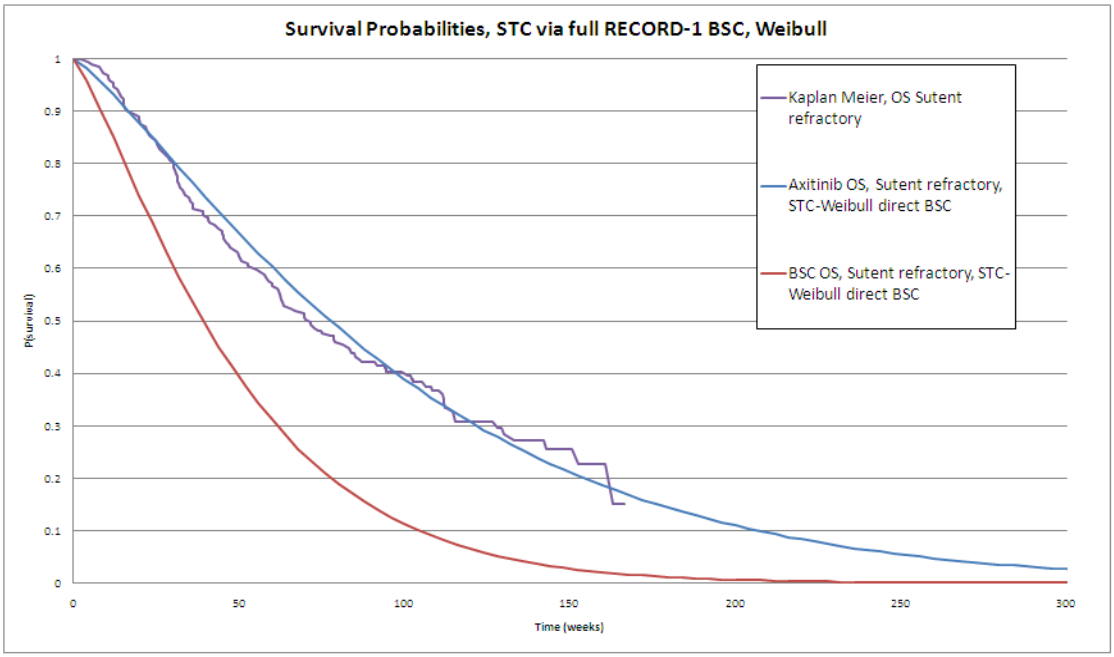
[redacted] Figure 24 and Figure 25 display the STC survival probabilities for the lognormal and Weibull models, respectively.

Figure 24: Lognormal OS distribution via RECORD-1 ITT placebo population if both treatments had been included in AXIS RCT



Abbreviations: BSC, best supportive care; OS, overall survival; STC, simulated treatment comparison.

Figure 25: Weibull OS distribution via RECORD-1 ITT placebo population if both treatments had been included in AXIS RCT



Abbreviations: BSC, best supportive care; OS, overall survival; STC, simulated treatment comparison.

Calibrated OS for axitinib-like placebo patients – RECORD-1 prior sunitinib everolimus

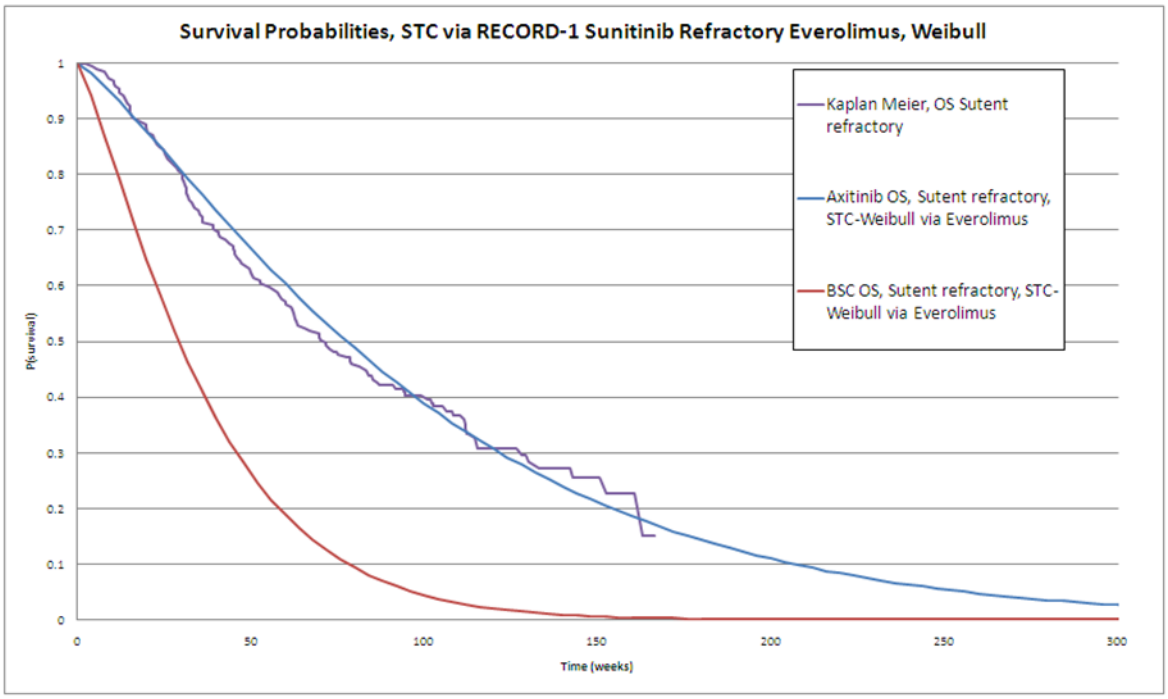
Lognormal distribution: The derived adjustment factor calculated for the RECORD-1 sunitinib-refractory everolimus population was [redacted], corresponding to a median of 46 weeks (10.6 months) for axitinib like patients if they were to receive everolimus.

Weibull distribution: The derived adjustment factor was [redacted], corresponding to the predicted median of 45.4 weeks (10.5 months).

[redacted]

To create a modelled placebo arm for the everolimus prior sunitinib population, the RPSFT-adjusted OS hazard ratio from the RECORD-1 study (0.53) was applied to the AXIS-like everolimus curve to generate a modelled AXIS-like, sunitinib refractory placebo curve. The RPSFT-adjusted hazard ratio was chosen as it was validated by the NICE ERG during the everolimus appraisal and was used to derive the final OS estimate included in the everolimus economic model (39). As the lognormal model does not support the application of a hazard ratio, the Weibull was the only option explored in the model. Figure 26 displays the survival probabilities calculated using this approach.

Figure 26: Weibull OS distribution via RECORD-1 prior sunitinib everolimus + RPSFT HR if both treatments had been included in AXIS RCT



Abbreviations: BSC, best supportive care; OS, overall survival; STC, simulated treatment comparison.

A summary of predicted STC survival times for OS is presented in Table 25.

Table 25: Summary of Predicted (Mean and Median) STC Survival Times: OS

	Observed median (months)	Predicted median with Weibull (months)	Predicted median with Lognormal (months)	Difference in mean (Weibull / Lognormal)
ITT placebo	10.0	8.2	8.3	[redacted]
Prior sunitinib everolimus	12.6	10.5	10.6	[redacted]

Abbreviations: ITT, intent-to-treat.

Conclusion

An STC is a useful tool for overcoming limitations in an evidence network when trials are generally comparable and patient characteristics are reported so that heterogeneity can be taken into consideration. Two studies were included in the STC; AXIS and RECORD-1 which compared the relative efficacy of everolimus vs placebo in patients that had received prior sunitinib therapy. The STC also suggested a beneficial treatment effect of axitinib compared with BSC in prior sunitinib patients with an estimated [redacted] in patients that received prior sunitinib treatment.

Although the STC method allows a comparison of prior sunitinib treated patients from the AXIS trial and the RECORD-1 trial without linking through the TARGET trial (which contained cytokine refractory patients only), there is some uncertainty around the results obtained due to assumptions that were required:

Despite some similarities between RECORD-1 and AXIS in terms of prior treatment, there are several differences between the two trials which could potentially confound the comparison. First, in contrast to AXIS, where all patients included in the study were required to have progressed on first-line therapy by RECIST-defined criteria, in the overall RECORD-1 population, 14% of patients (n=58) discontinued previous TKI therapy because of unacceptable toxicity. Among the subgroup of 58 patients who were intolerant to previous TKI therapy, 45 patients and 13 patients were randomly assigned to everolimus and placebo, respectively. Thus, patients in the RECORD-1 study could have discontinued prior treatment due to intolerance.

Second, in contrast to the AXIS study, where patients were required to have received only one prior therapy (sunitinib or a cytokine, or bevacuzimab + interferon-α or temsirolimus), patients in the RECORD-1 study may have received more than one previous therapy and could have been treated with sunitinib or sorafenib, as well as a cytokine in many cases (see Section 6.7.2).

The differences in the number and type of previous therapies between AXIS and RECORD-1 are a source of uncertainty when comparing the two trials using the STC framework. Also, the impact of this difference is difficult to determine and could potentially bias the comparison in several ways. For example, if a patient receives multiple lines of therapy it could potentially indicate a better response to treatment or a more slowly progressing course of disease, and thus a better prognosis of RECORD-1 patients compared to AXIS. However, this could also indicate a more progressed patient having had several lines of treatment with a lower expected survival and less likely to benefit from additional lines of treatment. As the prognostic MSKCC scores of patients in the RECORD-1 study were more favourable than those in AXIS at the start of the study, it is possible that the former is true. In addition, the difference in prior therapies between the two trials may have been taken into account when adjusting for differences in MSKCC scores however, this cannot be confirmed.

Thus, the inclusion of these patients in RECORD-1 would be expected to overestimate the survival of patients in favour of RECORD-1 compared to AXIS, and thus result in a more conservative incremental efficacy estimate of axitinib versus BSC.

Another consideration in comparing the two studies is that RECORD-1 study patients were allowed to have received previous treatment with sorafenib as well as sunitinib. When attempting to compare the axitinib sunitinib-refractory arm from AXIS with the BSC prior sunitinib sub-population from RECORD 1, the ideal RECORD-1 population for comparison would have consisted of those patients in the BSC arm that had progressed on sunitinib after receiving only one line of therapy. However, while an exploratory analysis of a small subgroup of prior sunitinib only patients (n = 56) in the RECORD-1 has reported a median PFS of 4.6 months with everolimus (n = 43) and 1.8 months with placebo (n = 13) (HR, 0.22; 95% CI, 0.09–0.55; P < .001), the median OS and patient characteristics have never been reported for this population. The closest available patient populations reporting overall survival data to allow the STC comparison were the ITT BSC population (corrected for crossover using the RPSFT method) and patients receiving everolimus treatment with only prior sunitinib therapy.

- There was heterogeneity between patients in the AXIS trial and the RECORD-1 trial in terms of prior treatment regimen. The sunitinib-refractory population in the

AXIS trial had received one previous treatment only, whereas 65% of prior sunitinib patients in RECORD-1 had received two prior treatments. As patient level data were not available for the RECORD-1 trial this heterogeneity could not be addressed. The impact of this difference was difficult to determine. For example, if a patient receives multiple lines of therapy it could potentially indicate a better response to treatment or a more slowly progressing course of disease, and thus a better prognosis. However, this could also indicate a more progressed patient who would be less likely to benefit from additional lines of treatment.

- In addition, in contrast to AXIS, where all patients progressed on first-line therapy by RECIST-defined criteria, in the overall RECORD-1 population, 14% of patients discontinued previous VEGFR-TKI therapy because of unacceptable toxicity.
- Furthermore, as the MSKCC scores of patients in the RECORD-1 study were more favourable than those in AXIS study at baseline, it is possible that patients in the RECORD-1 study performed better than would be expected than the patient population in the AXIS study.
- As patient level data were not available from the RECORD-1 trial, it was necessary to assume that everolimus and placebo followed the same survival functional form as axitinib in the AXIS trial and the validity of this assumption could not be verified.
- It was also assumed that all patient characteristics that could have accounted for differences in response to treatment were taken into consideration, i.e. that there were no unmeasured confounding factors, and that the effect of predictors would be the same in both the AXIS and RECORD-1 studies.
- Published data from RECORD-1 did not report patient characteristics and median OS for the prior sunitinib subgroup that received placebo. It was therefore necessary to assume equivalence between the prior sunitinib subgroup and the whole BSC treatment arm. Motzer 2010 (97) indicated that patients who failed first-line sunitinib treatment had worse OS than patients that had received other first line treatments, therefore the assumption that the prior sunitinib population was equivalent to the whole BSC population is likely to be conservative.
- Another potential limitation of the methodology is the variance in the absolute survival predictions between the lognormal and Weibull distributions. Even though these distributions predict very different long-term OS and PFS values, the difference in mean OS and PFS between axitinib and comparator are very similar, regardless of the distributional assumptions.
- The analysis assumes the RPSFT analysis used to correct for crossover in the RECORD-1 study was applied correctly, an assumption which is strengthened by the independent review of the method carried out by the NICE evidence review group. Also, any adjustment for patient cross-over introduces additional uncertainty in the estimated OS for BSC

In spite of the assumptions that were required, RECORD-1 was the only RCT identified in the systematic review that compared the efficacy of an active treatment vs placebo following failure of sunitinib treatment. Therefore, this method was considered the most appropriate to provide an adjusted comparison of efficacy between the AXIS sunitinib-refractory arm and the RECORD-1 prior sunitinib arm.

6.7.12 *Database analysis*

To further support the STC analysis, a non-RCT evidence source was considered to determine the relative efficacy of sorafenib and BSC in a sunitinib refractory population, thereby replacing the missing comparison in the evidence network and allowing a valid axitinib-BSC sunitinib refractory indirect comparison to be made. As the systematic review reported in Section 6.1 indicates, no RCT or non-RCT evidence was identified comparing sorafenib to BSC in a sunitinib-refractory population. Thus, a de-novo analysis was carried out using a retrospective national claims database to estimate the incremental OS benefit of sorafenib vs. BSC in a retrospective, non-interventional study framework.

The study utilised in this submission is a sub-analysis of a larger retrospective, non-interventional study carried out using data collected and stored in three comprehensive linked registries by the National Board of Health and Welfare, Stockholm, Sweden (see Table 26 below for a description of the registries included). This study, known as the the RENal COMParison (RENCOMP) study, has been previously published; a description of the methodology employed and results of the larger study have been reported previously (101, 102) and are provided as an appendix to this submission.

Table 26: Summary of National Swedish Registries used in the RENCOMP study

Registry	Year Founded	Data	% of population covered
Swedish Cancer Register (103)	1958	Diagnosis and death records for all patients with a cancer diagnosis	100
National Patient Register (104)	1987	Information on inpatient visits (since 1987) and outpatient visits (since 2001)	>90
Swedish Prescribed Drug Register (105)	2005	Dates and amounts of prescribed and dispensed drugs for individual patients	100

To estimate the relative efficacy of sorafenib vs. BSC on overall survival, this study examines real-world retrospective data to compare the OS of patients who received either sunitinib followed by sorafenib with those who received sunitinib followed by BSC. The current analysis includes 135 patients who were identified with advanced/mRCC and were recorded as having received first-line treatment with sunitinib after the introduction of TKIs in Sweden in 2006.

In order to correct for confounding factors (i.e. patient characteristics that may have been different between the two treatment arms in the database), a multivariate Cox proportional regression analysis was performed to create adjusted hazard ratios for sorafenib vs BSC in the second-line setting.

Covariates tested in the model were aligned with those included in two previous RENCOMP publications (101, 102), with several additional covariates included based on alignment with known mRCC prognostic factors typically included in clinical trials. The regression model included the following covariates:

Lead Time for Diagnosis: In accordance with Motzer criteria for mRCC, a dummy variable for the lead time between RCC diagnoses and mRCC was constructed and denoted 'Lead time RCC-met (1 year +, vs < 1year). A longer interval between RCC diagnosis and metastatic disease would indicate healthier patients and imply a longer chance of survival.

Age: A dummy variable for age defined as 'Age_met_65' which was =1 if age was greater than 65 at the start of second-line treatment, and =0 if age was 65 years or less at the start of treatment. A higher age would imply a lower OS.

Lead Time for Treatment: There is a wait and see tradition in mRCC treatment for patients that have a good prognosis (e.g. indolent disease, minimal metastatic sites, good performance status). Therefore, the variable 'Leadtime_mRCC_firstpre' was constructed with a value = 1 if lead time was less than 1 year and = 0 if lead time was 1 year or longer. A shorter lead time would hence indicate sicker patients with lower survival chances.

Duration of Sunitinib Treatment: A longer duration of sunitinib treatment may indicate stronger likelihood of survival in the second-line setting, as demonstrated in the patient level data analysis of the AXIS sunitinib refractory patients (see Section 6.7.11). Therefore a dummy variable was constructed to account for this, defined as 'Days of SU treatment' = 1 if duration was 90 days (3 months) or more and < 1 if duration was less than 3 months.

The results and explanatory power of the analysis may be affected by the number of variables included in the model. The choice of variables incorporated in the base-case model was aligned with variables reported as significantly affecting OS in the previous RENCOMP publications. Sensitivity analysis for different combinations of explanatory variables was carried out to examine the model for robustness.

Patient characteristics are detailed in Table 27. Characteristics such as gender, age and nephrectomy were similar between the two treatment groups. However, several variables indicated a healthier BSC population at baseline. These included:

- Year of RCC diagnosis: 35.7% of patients that received BSC were diagnosed with RCC before the introduction of TKIs (pre 2005), in comparison with 14.8% of patients that received sorafenib second-line. BSC patients were somewhat earlier diagnosed with mRCC, but the difference was much smaller. Hence, the data showed that BSC patients develop metastatic disease much later after diagnosis, potentially indicating a better prognosis for the BSC population.
- The lead time between mRCC and first prescription with sunitinib was longer for BSC patients (therefore potentially favouring BSC patients).
- A higher proportion of patients treated with sorafenib (35.6%) had a diagnosis of primary metastatic disease (M1) compared with BSC patients (26.3%) indicating a less favourable prognosis for patients that received sorafenib compared with patients that received BSC. However, there may have been underreporting of M1 status in the earlier years of the database and the difference may not be as high as it appeared from the available data.
- A higher number of patients that received BSC were treated at large institutions compared with those that received sorafenib. In previous RENCOMP analyses,

treatment at a large institution correlated with longer survival. More patients in the west region received sorafenib treatment, an area that was associated with lower survival. These differences potentially favour BSC patients.

Table 27: Patient characteristics - RENCOMP

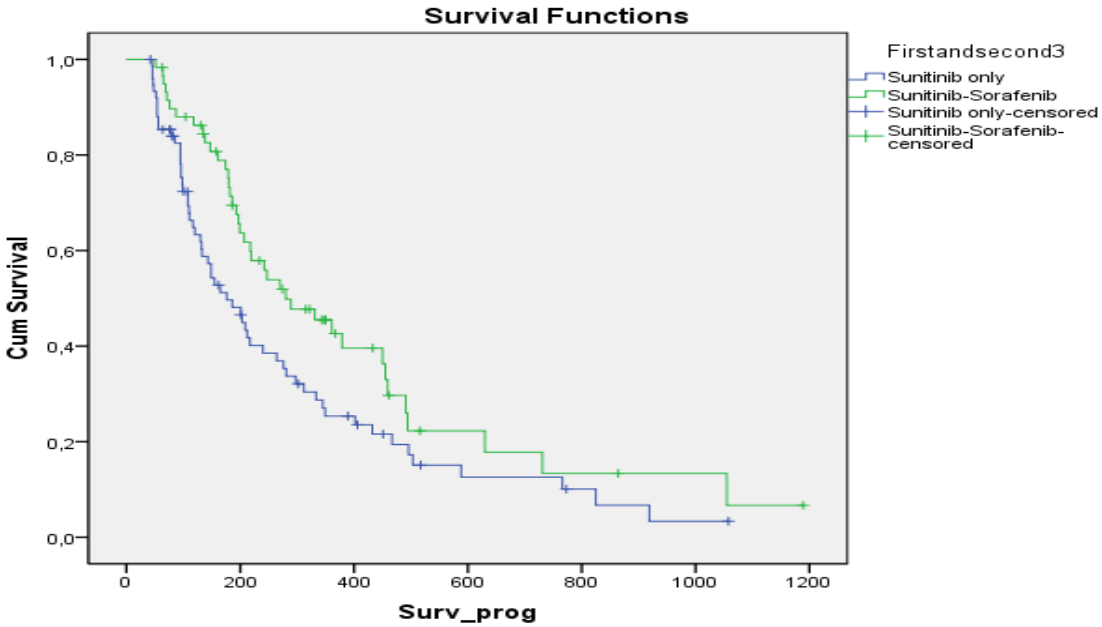
	Sorafenib N=59	BSC N=76
Male, %	72.9	69.7
Nephrectomy, %	79.7	75.0
>65 years of age at second-line treatment, %	62.7	53.9
RCC diagnosed 2000-2005, %	14.8	35.7
RCC diagnosed 2006-2008, %	85.2	64.3
mRCC diagnosed 2000-2005, %	5.1	9.9
mRCC diagnosed 2006-2009, %	89.8	86.8
Days_since_RCC_met < 1 year, %	64.4	56.6
M1 at diagnosis, %	35.6	26.3
Leadtime_mRCC_firstpre_ <1 year, %	83.1	75.0
>90 days sunitinib treatment, %	84.7	56.5
Treated at a large institution, %	33.9	40.8
Region, %		
South region	25.4	34.2
Mid Central Region	6.8	6.6
Stockholm Region	27.1	25.0
East Region	3.4	5.3
North Region	8.5	13.2
West Region	28.8	15.8

Abbreviations: BSC, best supportive care; mRCC, metastatic renal cell carcinoma; RCC, renal cell carcinoma.

Appendix 17 includes further information on patient characteristics in the two arms including dosing, number of prescriptions and treatment length (Table 69 and Table 70) and inpatient/outpatient resource utilisation (Table 71). The median (mean) OS for sunitinib refractory patients receiving BSC was 176 (289) days, approximately 5.8 (9.5) months. The median (mean) OS for sunitinib refractory patients receiving sorafenib was 280 (410) days, approximately 9.2 (13.5) months. The median (mean) OS for the total population was 218 (347) days, approximately 7.2 (11.4) months.

The OS HR between the two populations prior to adjustment for covariates was 0.640 (0.426; 0.961), p=0.031. Hence, patients treated with sorafenib had a 36% risk reduction of death compared to BSC in the second-line setting. Appendix 17 (Table 72) includes a full breakdown of unadjusted mean and median survival times for the two treatment arms in tabular format. Kaplan-Meier curves for OS are presented in Figure 27.

Figure 27: Kaplan-Meier analysis of OS in sunitinib refractory patients



A multivariate Cox proportional regression analysis was performed using variables with significance at the 5% level to correct for uncertainty. The results are presented in Table 28. The base case model, including only those variables significant at the 95% level, resulted in an OS HR of 0.621, and was statistically significant (9% CI: 0.412-0.936, p=0.023). Other variables resulted in HRs in accordance with expectations and were in line with results from previous RENCOMP publications. In general and as expected, most individual estimates except for nephrectomy were not statistically significant, likely due a low number of observations (n=135 patients) and therefore power.

Additional sensitivity analyses were performed to test the model assumptions – these are presented in Appendix 17 (Table 73). Analyses showed that regardless of the model chosen, HRs were robust, ranging from 0.580-0.712).

Table 28: Multivariate Cox proportional-hazards regression analysis

	Base case	
	Hazard ratio (95% CI)	**P value**
Second-line treatment (sorafenib vs BSC)	0.621 (0,412, 0,936)	0.023
Age 2nd line treatment start (age ≥ 65 vs <65)	0.754 (0.496, 1.144)	0.754
Gender (female vs male)	0.747 (0.460, 1.213)	0.239
Nephrectomy (yes vs no)	0.509 (0.317, 0.817)	0.005
Lead time between RCC and mRCC (≥ 1 year vs <1 year	0.629 (0.405, 0.979)	0.040

Abbreviations: BSC best supportive care; CI confidence interval; mRCC, metastatic renal cell carcinoma; RCC, renal cell carcinoma.

An indirect comparison was conducted by incorporating the RENCOMP hazard ratio into a meta-analysis, using the sunitinib refractory OS hazard ratio from the AXIS study (0.997, 95% CI 0.782, 1.27) to generate an axitinib-BSC OS hazard ratio. The methodology of the indirect comparison was identical to that presented in Section 6.7.5, but TARGET hazard ratios were substituted for RENCOMP hazard ratios (Figure 28).

Figure 28: Network diagram for the indirect comparison of axitinib with BSC using RENCOMP data

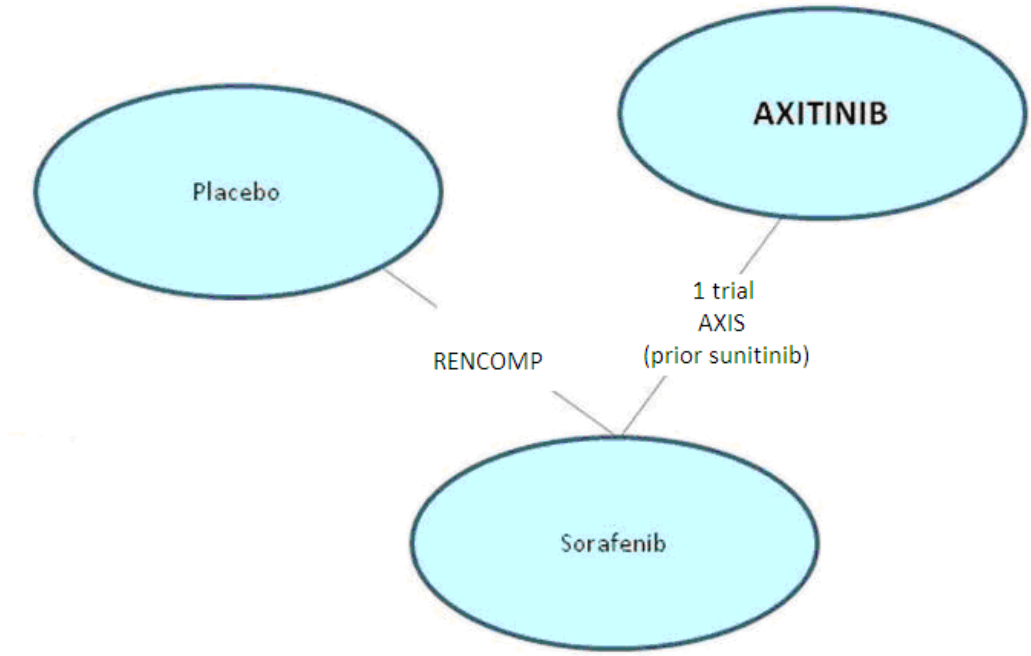


Table 29: Estimated hazard ratio of axitinib vs BSC – using RENCOMP data

	OS HR (95% CI)
Base Case RENCOMP Model	0.619 (0.384-0.997)

Abbreviations: BSC, best supportive care; HR, hazard ratio; OS, overall survival.

Conclusion

While observational study data are considered to be a lower-quality source of evidence than RCT evidence in terms of the NICE reference case, the lack of RCT evidence to complete the indirect comparison network meant that exploration of additional sources of evidence were required. Furthermore, numerous HTA experts (including Sir Michael Rawlins, Chairman of NICE) have affirmed the usefulness of observational evidence to reinforce and augment RCT evidence where RCT evidence is unavailable or incomplete (106). An additional advantage of the RENCOMP data is that, as opposed to the current AXIS RCT data, it is significantly more mature and thus potentially more representative of long-term survival trends.

However, the inclusion of observational data in an indirect comparison with RCT data is a potential source of uncertainty. For example, it was not known whether patients in the RENCOMP database had discontinued first-line treatment due to disease progression or toxicity, therefore there may have been heterogeneity between patients at baseline.

Despite the heterogeneity in patient characteristics and the different treatment settings (clinical trial vs real-world) between the AXIS trial and the RENCOMP analysis, it is reasonable to assume that the proportional efficacy of adding sorafenib to BSC, calculated via hazard ratios, would be similar between the two settings. In addition, this additional analysis allowed a further comparison of OS with axitinib vs BSC in a sunitinib refractory population.

The use of RENCOMP data corrects one of the main inconsistencies in the evidence network: the lack of sorafenib or BSC data in the sunitinib refractory population. However, it should be noted that this analysis does not correct for the other key limitation of the evidence network, the confounding in the OS estimate between the axitinib and sorafenib treatment arms in the AXIS study. As is discussed in further detail below in Section 6.10.2, the measurement of OS in the AXIS study is subject to a number of substantial limitations including the inherent difficulty of demonstrating incremental OS benefit in an oncology trial, the potential masking of OS benefit due to the use of an active comparator, and confounding by the administration of non-randomised post-study treatment, and confounding due to survival post-progression.

Additional limitations of this analysis included:

- The sample size of the RENCOMP analysis (59 for sorafenib and 76 for BSC) is small. However, this issue is somewhat addressed due to the incorporation of the uncertainty in the estimated OS HR from RENCOMP in the economic model of axitinib vs. BSC, as represented by the confidence intervals in Table 32. PFS was not recorded in the RENCOMP study and therefore is not known precisely.
- For the calculation of Kaplan-Meier curves, it was assumed that progression started at 40 days after the last package of sunitinib was dispensed. The most commonly dispensed package is the 50 mg/28 tablets. As the drug cost is high, the majority of patients receive one package at a time and the next package after radiological and/or clinical confirmation of non-progressive disease. Hence, if treatment stopped due to progression it is likely that this occurred sometime within these 40 days.
- As the RENCOMP database is meant to track general health conditions at the national level and not designed specifically for advanced/mRCC, it was not possible to adjust for all patient characteristics typically reported in an advanced/mRCC trial, such as MKSCC or ECOG. By studying available information on potential differences between the populations and including important prognostic variables in the multivariate this limitation was addressed as far as possible.
- The analysis was based on data for patients diagnosed no later than 2008, hence reflecting a time period with less experience of treating patients with the new targeted therapies.

6.8 Non-RCT evidence

6.8.1 ***If non-RCT evidence is considered (see Section 6.2.7), please repeat the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for***

undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in Sections 10.6 and 10.7, appendices 6 and 7.

For details of non-RCT evidence for axitinib, please refer to Section 10.18 (Appendix 18)

6.9 Adverse events

Summary of safety

- The pivotal Phase III trial (AXIS) demonstrated an adverse event profile reflective of the mechanism of action of axitinib.
  - The most common treatment-emergent AEs (all grades) in the axitinib arm were diarrhoea (54.9%), hypertension (40.4%) and fatigue (39.0%).
  - Palmar-plantar erythrodysaesthesia (hand foot syndrome) was less common in the axitinib arm (27.3%) compared with the sorafenib arm (51.0%).
  - More patients that received axitinib treatment experienced hypertension (40.4%) compared with patients that received sorafenib (29.0%), however most cases were mild or moderate.
  - Axitinib was associated with fewer Grade 3 and 4 treatment-related AEs compared with sorafenib.
  - Grade 3 AEs were reported by 45.1% of patients in the axitinib arm and 47% of patients in the sorafenib arm.
  - Grade 4 AEs were reported by 3.1% of patients in the axitinib arm and 5.4% of patients in the sorafenib arm.
  - The most frequently reported Grade 3 AEs in the axitinib arm were hypertension (15.3%), diarrhoea (9.7%) and fatigue (9.5%).
  - The incidence of SAEs was similar between treatment groups (30.1% in the axitinib arm and 31% in the sorafenib arm).
  - Axitinib treatment was associated with fewer AEs leading to dose modification, temporary delay or permanent discontinuation than sorafenib treatment.
  - In the axitinib arm, 55.4% of patients experienced AEs leading to dose modification or temporary delay in treatment compared with 62.0% of patients in the sorafenib arm.
  - In the axitinib arm, 3.9% of patients permanently discontinued the study due to treatment-related AEs compared with 8.2% in the sorafenib arm.
- The supporting Phase II studies provided additional evidence to support the safety profile of axitinib in cytokine- and sorafenib-refractory patients with advanced/mRCC.
  - In cytokine-refractory patients, the incidence of palmar-plantar erythrodysaesthesia and proteinuria were reported more commonly in the Japan-based study (A4061035) that in the USA/European-based study (A4061012).

The identification of clinical evidence is described in Sections 6.1 and 6.2. All trials relevant to this submission are listed in Table 3 in Section 6.2.4 and Table 4 in Section 6.2.7. There were no relevant RCT studies designe*d* primarily to assess the safety of axitinib. The main adverse event evidence is drawn from the pivotal Phase III RCT

(AXIS) and is presented in Section 6.9.2. Additional supportive safety evidence from non-RCT Phase II studies are also briefly described in this section.

6.9.1 ***If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.***

None

6.9.2 ***Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event.***

AXIS (A4061032)

Adverse events (AEs) were recorded in the AXIS pivotal trial, which was designed to primarily assess efficacy. An AE was defined as any untoward medical occurrence in a patient during the study, irrespective of whether the event was considered to have a causal relationship with the study treatment. The Investigator obtained and recorded all observed or volunteered AEs, the severity of the event and the Investigator's opinion of the relationship to the study treatment. AEs included adverse drug reactions, illnesses with onset during the study and exacerbation of previous illnesses. In addition, clinically significant changes in physical examination findings and abnormal objective test findings were classed as AEs.

An overall summary of AEs by treatment for the safety analysis set (SA) is presented in Table 30.

Table 30: Summary of adverse events (SA set)

Adverse events Number (%) subjects	Axitinib N=359	Sorafenib N=355
Patients with AEs†	342 (95.3)	347 (97.7)
≥ 1 treatment related AE	325 (90.5)	336 (94.6)
≥ 1 SAE	108 (30.1)	110 (31.0)
≥ 1 treatment related SAE	44 (12.3)	43 (12.1)
Deaths due to AEs‡ (all causality)	34 (9.5)	24 (6.8)
Discontinuation due to AEs (all causality)	33 (9.2)	46 (13.0)
AEs of special interest (all causality)		
AEs that led to dose reduction	95 (26.5)	73 (20.6)
AEs that led to temporary discontinuation	199 (55.4)	220 (62.0)

Abbreviations: AE, adverse event; SA, safety analysis; SAE, serious adverse event.
†According to Medical Dictionary for Regulatory Activities (MedRA) version 13.1; ‡ Grade 5 adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Treatment-emergent adverse events (TEAEs) occurring in at least 5% of patients in either arm are presented in Table 31. The most frequently reported TEAEs (all-causality) were:

- Diarrhoea (54.9%), hypertension (40.4%) and fatigue (39.0%) in the axitinib arm
- Diarrhoea (53.2%), palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) (51.0%) and alopecia (32.4%) in the sorafenib arm.

TEAEs that occurred with a higher frequency (≥ 10 percentage points) within a treatment arm were:

- Hypertension, dysphonia, nausea, and hypothyroidism in the axitinib arm
- Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome), rash, and alopecia in the sorafenib arm.

Table 31: Treatment-emergent adverse events occurring in ≥ 5% of patients

MedDRA preferred term	Axitinib N=359 n (%)	Sorafenib N=355 n (%)
Total subjects with ≥ 1 TEAE	333 (92.8)	341 (96.1)
Diarrhoea	197 (54.9)	189 (53.2)
Hypertension	145 (40.4)	103 (29.0)
Fatigue	140 (39.0)	112 (31.5)
Decreased appetite	123 (34.3)	101 (28.5)
Nausea	116 (32.3)	77 (21.7)
Dysphonia	111 (30.9)	48 (13.5)
Palmar-plantar erythrodysaesthesia syndrome	98 (27.3)	181 (51.0)
Weight decreased	89 (24.8)	74 (20.8)
Vomiting	85 (23.7)	61 (17.2)

MedDRA preferred term	Axitinib N=359 n (%)	Sorafenib N=355 n (%)
Asthenia	74 (20.6)	50 (14.1)
Constipation	73 (20.3)	72 (20.3)
Hypothyroidism	69 (19.2)	29 (8.2)
Cough	55 (15.3)	59 (16.6)
Mucosal inflammation	55 (15.3)	44 (12.4)
Arthralgia	54 (15.0)	39 (11.0)
Stomatitis	54 (15.0)	44 (12.4)
Dyspnoea	53 (14.8)	43 (12.1)
Abdominal pain	51 (14.2)	38 (10.7)
Back pain	50 (13.9)	46 (13.0)
Headache	50 (13.9)	40 (11.3)
Pain in extremity	45 (12.5)	48 (13.5)
Rash	45 (12.5)	112 (31.5)
Proteinuria	39 (10.9)	26 (7.3)
Dysgeusia	38 (10.6)	29 (8.2)
Dry skin	36 (10.0)	38 (10.7)
Dyspepsia	36 (10.0)	8 (2.3)
Dizziness	33 (9.2)	15 (4.2)
Abdominal pain upper	29 (8.1)	14 (3.9)
Insomnia	29 (8.1)	18 (5.1)
Myalgia	25 (7.0)	10 (2.8)
Pyrexia	25 (7.0)	37 (10.4)
Pruritus	24 (6.7)	44 (12.4)
Dehydration	23 (6.4)	9 (2.5)
Disease progression	23 (6.4)	14 (3.9)
Epistaxis	22 (6.1)	15 (4.2)
Oropharyngeal pain	20 (5.6)	19 (5.4)
Chest pain	19 (5.3)	16 (4.5)
Flatulence	19 (5.3)	8 (2.3)
Hypotension	19 (5.3)	10 (2.8)
Musculoskeletal pain	19 (5.3)	21 (5.9)
Pain	19 (5.3)	15 (4.2)
Oedema peripheral	17 (4.7)	20 (5.6)
Alopecia	14 (3.9)	115 (32.4)
Anaemia	13 (3.6)	41 (11.5)
Lipase increased	9 (2.5)	19 (5.4)

MedDRA preferred term	Axitinib N=359 n (%)	Sorafenib N=355 n (%)
Erythema	8 (2.2)	36 (10.1)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Grade 3 and 4 adverse events

In the axitinib treatment arm, 50.4% of patients had Grade 3 AEs and 5.8% had Grade 4 AEs that were treatment-emergent. In the sorafenib treatment arm, 51.3% of patients had grade 3 AEs and 10.1% had Grade 4 AEs that were treatment-emergent.

The most common treatment-related Grade 3 and 4 AEs are presented in Table 32.

Table 32: Summary of the most common Grade 3 and 4 treatment-related adverse events (SA set)

MedDRA preferred term	Axitinib N=359		Sorafenib N=355	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	162 (45.1)	11 (3.1)	167 (47.0)	19 (5.4)
Diarrhoea	35 (9.7)	1 (0.3)	23 (6.5)	2 (0.6)
Hypertension	55 (15.3)	1 (0.3)	38 (10.7)	1 (0.3)
Fatigue	34 (9.5)	1 (0.3)	12 (3.4)	1 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	18 (5.0)	0	57 (16.1)	0

Abbreviations: AE, adverse event; MEdDRA, Medical Dictionary for Regulatory Activities; SA, safety analysis.

Clinical laboratory evaluations

Similar proportions of patients in the axitinib and sorafenib arms experienced Grade 3 or 4 haematology laboratory values, with the exception of haemoglobin levels. Fewer patients in the axitinib arm experienced decreased haemoglobin levels compared with patients in the sorafenib arm at Grade 3 (1 [0.3%] patient vs 11 [3.5%] patients, respectively) or Grade 4 (0 patients vs 1 [0.3%] patients, respectively).

Serious adverse events

A serious adverse event (SAE) was defined as any AE that resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity or resulted in congenital abnormalities/birth defects. In total, 30.1% of patients in the axitinib arm experienced SAEs, of which 12.3% were considered to have treatment-related SAEs; those judged by the investigator to be at least possibly related to the study drug. In the sorafenib arm, 30.1% of patients experienced SAEs, of which 12.1% were considered to be at least possibly related to study treatment.

The most frequently reported treatment-related SAEs in the axitinib arm were dehydration and diarrhoea, experienced by 1.9% and 1.7% of patients, respectively. The most frequently reported treatment-related SAEs in the sorafenib arm were anaemia, diarrhoea, pyrexia, and erythema multiforme, each experienced by 0.8% of patients.

Deaths

In total, 113 (31.5%) patients in the axitinib arm of the SA set died; 35 (9.7%) died during the study and 78 (21.7%) died during follow-up. In the sorafenib arm, 109 (30.7%) patients died, 6.5% died during the study and 24.2% died during follow-up.

AEs leading to dose reductions or interruptions

In total, 55.4% of patients in the axitinib arm experienced AEs leading to dose modification or temporary delay of treatment; the most common AEs were diarrhoea (14.5%) and hypertension (12.8%). In the sorafenib arm, 62.0% of patients experienced AEs leading to dose modification or temporary delay of treatment; the most common AEs were palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) (17.7%) and diarrhoea (9.3%).

AEs leading to permanent discontinuation of study medication

AEs that led to study discontinuation were experienced by 9.2% of patients in the axitinib arm, of which 3.9% were considered to be treatment-related. AEs that led to study discontinuation were experienced by 13% of patients in the sorafenib arm, of which 8.2% were treatment-related. The most common AEs leading to discontinuation in the axitinib arm were disease progression (2.5%), fatigue (1.1%), and transient ischemic attack (0.8%). The most common AEs leading to discontinuation in the sorafenib arm were disease progression (1.1%), palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) (1.1%), diarrhoea (0.8%) and asthenia (0.8%).

Adverse events from non-RCT studies (A4061012, A4061023, A4061035)

AEs reported in the Phase II studies were similar to those reported in the pivotal AXIS trial. In study **A4061012** (52), the most common treatment-related AEs reported by axitinib treated cytokine-refractory patients were diarrhoea (60%), hypertension (58%), fatigue (52%) and nausea (44%). The most common Grade 3/4 treatment-related AEs were fatigue (15%), diarrhoea (10%) and nausea (8%).

In sorafenib-refractory patients (**A4061023**) (42), the majority of AEs were mild or moderate in intensity (Grade 1 or 2). The most common all-causality non-haematologic AEs of any grade were fatigue (77.4%), diarrhoea (61.3%), anorexia (48.4%) and hypertension (45.2%). The most common Grade 3 AEs were palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) (16.1%), fatigue (16.1%), hypertension (16.1%), and diarrhoea (14.5%).

There were some notable differences in the most common AEs experienced in the cytokine-refractory Japanese patient population (**A4061035**) (53). The most common treatment-related non-haematologic AEs were hypertension (84%), palmar-plantar erythrodysaesthesia syndrome (75%) (hand-foot syndrome), diarrhoea (64%) and proteinuria (58%). The most common Grade 3/4 AEs were hypertension (70%), palmar-plantar erythrodysaesthesia syndrome (22%) and proteinuria (9%). In total, 28% of

patients developed proteinuria ≥ 2 g/24 h requiring dose reduction or treatment interruption/discontinuation.

The incidence of proteinuria and palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) was higher in Japanese patients in study A4061035 compared with the Western study of axitinib for cytokine-refractory mRCC A4061012. In contrast, the incidence of dry skin was higher in the Western study (33% vs 5%). Axitinib dose reductions were required in more Japanese patients (66%) than Western patients (29%) with cytokine-refractory mRCC.

6.9.3 *Give a brief overview of the safety of the technology in relation to the decision problem*

Please refer to the summary box at the start of Section 6.9 for a review of the safety profile of axitinib.

6.10 Interpretation of clinical evidence

6.10.1 *Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.*

The clinical benefit of axitinib has been demonstrated in the pivotal Phase III RCT, AXIS. Supporting evidence was provided from three non-RCT studies and comparative evidence was provided by an indirect comparison, an STC and a database analysis. The pivotal trial (AXIS) demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint, PFS, compared with an active comparator (sorafenib). Patients were stratified to axitinib or sorafenib based on prior treatment regimen, with 54% in each treatment group having received prior sunitinib therapy and 35% in each group having received prior cytokine therapy (the remaining patients received prior temsirolimus or bevacizumab + IFN-α).

The statistically significant improvement in PFS was observed in each prior treatment subgroup. In sunitinib-refractory patients, median PFS was 4.8 months in the axitinib arm compared with 3.4 months in the sorafenib arm (p=0.0107). In the cytokine-refractory subgroup, median PFS was 12.1 months in the axitinib arm compared with 6.5 months in the sorafenib arm (p<0.0001). Although the improvement in PFS with axitinib treatment was smaller in the sunitinib-refractory subgroup compared with the cytokine-refractory subgroup, there was a 26% reduction in the risk of progression or death for axitinib treated patients compared with sorafenib treated patients who received prior sunitinib treatment over the whole study period.

The sample size for the pivotal trial was calculated based on 90% power to show improvement in PFS using a log-rank test with an overall 1-sided significance level of 0.025 in the ITT population. The trial was not powered to detect significance in the suntinib-refractory and cytokine-refractory subgroups due to the number of patients that would have been required. The lack of power to detect significance in the subgroups may have resulted in type I error (i.e. the null hypothesis that there is no difference between the two treatments was incorrectly rejected is true). However, both subgroup analyses demonstrated a statistically significant improvement in PFS with axitinib vs sorafenib at the 1.1% level or lower (sunitinib-refractory subgroup [p=0.0107], cytokine-refractory subgroup [p<0.0001]). The quality of the data was considered sufficient for the CHMP to give a positive recommendation for axitinib specifically for sunitinib-refractory and cytokine-refractory patient populations.

OS was a secondary endpoint in the AXIS trial. Patients treated with axitinib did not experience a significant benefit in OS compared with sorafenib treated patients. This observation is discussed further in Section 6.10.2.

The ORR was numerically higher but not statistically significant in the sunitinib refractory group (11.3% for axitinib treated patients vs 7.7% for sorafenib treated patients; p=0.1085) and was significantly higher in the cytokine group (32.5% of axitinib treated patients vs 13.6% of sorafenib treated patients; p=0.0002).

In the AXIS trial, patients remained on study treatment until they experienced disease progression. QoL (as measured by FKSI-15, FKSI-DRS and EQ-5D) was maintained whilst patients remained on axitinib and sorafenib treatment. At the end of treatment after

patients had progressed, QoL scores were substantially worse, suggesting that patients' QoL is maintained whilst they remain on treatment and free of disease progression. Patients in the AXIS trial received axitinib treatment for longer than sorafenib (median 186 days vs 141 days, respectively), suggesting that patients experienced a longer maintenance in QoL with axitinib treatment.

Adverse events reported for patients treated with axitinib in the pivotal Phase III trial were generally mild or moderate in severity and clinically manageable. The AE profile was consistent with the mechanism of action of axitinib. The most common treatment-emergent AEs experienced in the axitinib arm were diarrhoea (54.9%), hypertension (40.4%) and fatigue (39.0%), most of which were mild or moderate in severity.

The discontinuation rate due to treatment related AEs was lower for axitinib (3.9%) compared with sorafenib (8.2%) and fewer patients treated with axitinib experienced dose interruptions due to AEs (50.4%) compared with sorafenib (62.0%), suggesting that AEs associated with axitinib treatment were more well tolerated by patients compared with sorafenib.

Axitinib is the first, next generation TKI, designed to have greater potency and selectivity for VEGFRs than other currently available TKIs. These features are reflected in the statistically significant improvement in PFS over an active comparator, providing the rationale for the use of axitinib as an effective second-line therapy in patients that have developed resistance to first-line sunitinib or a cytokine. The clinically meaningful gain in PFS and ORR as well as the manageable AE profile also enables patients to maintain their QoL for longer.

6.10.2 *Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.*

The axitinib pivotal trial (AXIS) was the first study performed demonstrating the efficacy and safety of a targeted therapy for advanced/mRCC against an active comparator. The clinical evidence for axitinib was provided by an RCT, three non-RCTs, an indirect comparison, an STC and a retrospective database analysis.

Axitinib pivotal RCT (AXIS)

Due to known toxicity differences between axitinib and sorafenib (in particular the frequent occurrence of rash and palmar-planter erythrodysaesthesia syndrome with sorafenib treatment), it was not considered feasible to blind the study through use of a double-dummy methodology. Although an open-label study design was used, disease progression was assessed by a blinded IRC.

The AXIS trial excluded from enrolment patients that had received more than one prior systemic treatment. Patients were stratified based on prior treatment regimen, with the majority of patients enrolled having received sunitinib or cytokines as their first-line treatment and thus reflecting the licensed indication for axitinib. This also allowed subgroup analyses to be performed on patients that received first-line sunitinib treatment and first-line cytokine treatment. Cytokine-treated patients are considered by many clinicians to comprise a markedly different subgroup of patients to sunitinib-treated patients. The cytokine refractory patients may have failed first-line treatment sooner (90) and also as a TKI naïve population, may be an easier population to treat in a second-line

setting than those who had previously failed on sunitinib treatment (i.e. a TKI). Therefore it was considered relevant to perform a subgroup analysis.

The primary endpoint of PFS was approved by regulatory agencies as a relevant primary endpoint and was accepted by the CHMP as appropriate evidence to recommend that axitinib be granted a marketing authorisation. Nearly all pivotal trials for other licensed targeted therapies for advanced/mRCC have also used PFS as the primary endpoint, including sunitinib (107) and pazopanib (82), which have been approved by NICE as first-line treatment options (15, 34).

Axitinib showed significant improvement in PFS compared with sorafenib in the overall patient population, the sunitinib refractory subgroup and the cytokine refractory subgroup. As few patients respond to first-line treatment with cytokines, it would be expected that cytokine refractory patients may respond better to a subsequent TKI therapy compared with patients who received a first-line TKI. The improvement in PFS with axitinib compared with sorafenib in patients that received first-line sunitinib treatment also supports the rationale for the sequential use of TKIs in patients with advanced/mRCC and demonstrates the benefit of greater potency of axitinib for VEGFR-1, -2 and -3.

OS was a secondary endpoint in the AXIS trial. Despite having met the primary endpoint of significantly greater PFS compared with sorafenib, there was no significant difference in OS between the axitinib arm and the sorafenib arm at the final OS analysis in the overall population, the sunitinib-refractory subgroup or the cytokine refractory subgroup. Historically, it has been difficult to demonstrate a survival benefit in RCTs for targeted therapies in advanced/mRCC. Most therapies that have been approved by the EMA for the first- or second-line treatment of advanced/mRCC have not been able to demonstrate an OS benefit despite significant improvements in PFS, even where the comparator was placebo; this includes sunitinib and pazopanib, which are recommended by NICE for the first-line treatment of advanced/mRCC (15, 34).

Several confounding factors may influence the ability to detect a significant difference in OS, despite a significant improvement in PFS.

- The use of subsequent treatments after progression has occurred on the trial therapy can affect OS (108). Whist in the AXIS trial, cross-over was not permitted, following progression on either axitinib or sorafenib, patients were discontinued from treatment and subsequently received best supportive care or an alternative therapy in a non-randomised manner at the discretion of the Investigator (see Section 6.3.9).
- In the cytokine-refractory subgroup, 46.4% of patients in both the axitinib arm and in the sorafenib arm received subsequent treatment. In addition, 22.7% of patients in the axitinib arm and 20.0% of patients in the sorafenib arm received more than 1 subsequent treatment. In the sunitinib-refractory subgroup, 65.2% of patients in the sorafenib arm and 60.0% of patients in the axitinib arm received subsequent treatment. Additionally, 28.6% of patients in the axitinib arm and 33.2% of patients in the sorafenib arm received more than 1 subsequent treatment. It should be noted that whilst axitinib treated patients were able to receive sorafenib following study medication, sorafenib patients were not able to receive axitinib.
- As a result, OS was not determined solely by the effect of axitinib or sorafenib treatment and the two groups could not be accurately compared due to differences

in the number of patients receiving subsequent therapy and the type of therapy received. It is therefore difficult to make an accurate comparison of original randomised regimens on the basis of OS (83).

- The length of time that patients remain alive following progression may also affect OS outcomes. Broglio and Berry (2010) performed a simulation study comparing PFS with OS, taking into account the length of time that patients remained alive following disease progression (83). They reported that the longer that patients survive post-progression, the lower the probability of being able to demonstrate a statistically significant difference in OS. The authors concluded that for trials with a PFS benefit, a lack of statistical significance in OS does not mean a lack of improvement in OS (83). As patients in the axitinib pivotal trial remained alive for approximately a year after disease progression was documented, this may have had an impact on the OS analysis.
- The use of an active comparator in the AXIS trial may also have reduced the likelihood of observing a difference in OS. The incremental benefit in PFS observed with axitinib vs sorafenib was not as great as the benefit would have been if axitinib was compared with placebo. Broglio and Berry (2010) reported that the smaller the incremental benefit in PFS, the greater the number of patients that would be required to demonstrate a benefit in OS and increases the likelihood that random variation in sampling will mask the benefit (83). This problem is amplified when considering the cytokine refractory and sunitinib-refractory subgroups, as patient numbers (and in the case of the sunitinib refractory subgroup, incremental PFS) are lower than for the overall population. As RCTs for targeted therapies in advanced/mRCC have been unable to show an OS benefit compared with placebo, it is perhaps unsurprising that it was not possible to show a benefit of axitinib vs an active comparator and the current evidence likely underestimates the true OS benefit of axitinib.

Comparison with BSC

Cytokine-refractory patients

Indirect comparison

Due to a lack of clinical data on the relative efficacy of axitinib vs BSC, it was necessary to perform an indirect comparison to generate an axitinib-BSC hazard ratio. A systematic review was performed to identify RCT evidence on the efficacy and safety of axitinib and relevant comparators for the management of advanced/mRCC in the second-line setting. As the only RCT evidence for axitinib was provided by the AXIS trial (where axitinib was compared with sorafenib in patients receiving second-line treatment), it was necessary to identify RCTs which investigated the comparative efficacy of sorafenib vs placebo (BSC) in a second-line patient population who had received prior cytokine or prior sunitinib treatment.

The systematic review identified one RCT which compared the efficacy of sorafenib vs placebo in a second-line patient population (TARGET). In this study, 80% of patients received prior cytokine treatment. No patients in the TARGET study had received VEGF-TKI therapy, as their prior systemic treatment in the trial was reflective of the availability of these medicines at the time of trial design and initiation. This trial therefore provided a comparison for the cytokine refractory population from the AXIS trial, but precluded an

appropriate comparison with the sunitinib-refractory population, due to the differences in the treatments that patients received first-line. In addition, the TARGET trial did not correct for patient crossover in the OS analysis, which provides considerable uncertainty around the OS hazard ratios generated for the cytokine refractory population.

Suntinib-refractory patients

Simulated treatment comparison

The lack of clinical data for sorafenib versus BSC in a sunitinib-refractory population precluded an indirect comparison with this subgroup in the AXIS trial. Only one study was identified in the systematic review that compared the efficacy of a targeted therapy to placebo following TKI treatment. The RECORD-1 trial compared the efficacy of everolimus vs placebo in patients who had received one or more prior therapies,, including a subpopulation of patients that had received prior sunitinib.

In spite of the differences in patient populations, a further statistical analysis was performed in order to provide estimates for the relative efficacy of axitinib vs BSC in a sunitinib refractory population. The STC allowed the exclusion of the TARGET trial (which contained cytokine refractory patients only) from the analysis and allowed an adjusted side by side comparison of the efficacy of axitinib with BSC in patients that had received prior sunitinib. The results of the STC were associated with some uncertainty due to differences in the patient populations at baseline (i.e. patients in RECORD-1 may have received more than one previous treatment) and a lack of patient level data from the RECORD-1 trial (median values had to be used). However this method did allow the creation of an adjusted comparison between the sunitinib refractory patients treated with axitinib and BSC.

Database analysis (RENCOMP)

To further support the STC analysis, a retrospective analysis of real world OS data was performed from a subset of patients that received sorafenib treatment or BSC following failure of first-line sunitinib. This enabled the generation of HRs between sorafenib and BSC which were then substituted in the indirect comparison for the TARGET trial to obtain an OS HR for axitinib vs BSC in sunitinib-refractory patients. However, the inclusion of observational data in an indirect comparison with RCT data is a potential source of uncertainty.

Despite the limitations in the evidence network to perform a robust comparison of axitinib with BSC in patients that received prior sunitinib and prior cytokine treatment, the methods employed demonstrate a benefit of axitinib vs BSC in both patient populations.

In order to identify a link between axitinib and BSC for the sunitinib-refractory subgroup, an additional systematic review was performed to identify studies in which patients received first-line sunitinib treatment followed by BSC after they had experienced disease progression. However, no evidence was identified for the network of axitinib vs BSC in the sunitinib-refractory population. The systematic review did however provide evidence for the poor prognosis of patients who progress following first-line sunitinib treatment, with the two UK studies reporting similar median OS times of 4.1 months and 4.3 months (30, 31). The results further support the OS estimates from the STC and RENCOMP analyses.

6.10.3 *Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.*

Sorafenib was chosen as the comparator for the axitinib pivotal trial as the only drug approved in the EU with a second-line indication at the time of the AXIS study start-up (2008). While sorafenib is approved in second-line for a cytokine refractory population only, reflective of the TARGET study, and not approved in a VEGFR-TKI refractory population, several prospective phase 2 studies of sorafenib following prior VEGF-pathway inhibitors suggest that sequential treatment is a feasible and effective treatment option for patients with RCC (109-113) While not used widely in clinical practice in the second-line setting in the UK, sorafenib is and remains a widely used active therapy in second-line after failure of prior VEGFR-TKI therapy within the EU (Pfizer Ltd, data on file). In addition, it was the only drug not previously received by patients entering the study. Pfizer sought scientific advice regarding the design of the AXIS study from regulatory authorities in Sweden, Spain and Netherlands and confirmed the acceptability of sorafenib as a comparator. It was not considered ethical, with the availability of a licensed second-line medication, to provide patients with placebo. It was also considered that the use of an active comparator would provide a more robust analysis of the efficacy and safety of axitinib.

As no existing licensed second-line treatments for advanced/mRCC have been approved by NICE, the comparator outlined in the scope was BSC. A number of statistical analyses were undertaken in order to generate comparisons of the efficacy of axitinib compared with BSC, particularly in sunitinib-refractory patients who are considered to comprise the majority of the UK target population. Whilst there are limitations associated with these statistical analyses, these methods were considered the most appropriate considering the paucity of data regarding advanced/mRCC patients who received first-line sunitinib followed by BSC.

The primary endpoint of PFS was approved by regulatory agencies as a relevant primary endpoint and was accepted by the CHMP as appropriate evidence to recommend that axitinib be granted a marketing authorisation. In addition, the majority of pivotal trials for other licensed targeted therapies for RCC have also used PFS as the primary endpoint, including sunitinib (107) and pazopanib (82), which have been approved by NICE as first-line treatment options (15, 34). PFS is a relevant outcome for patients as they may experience a better quality of life for longer due to delayed disease progression and associated worsening of symptoms. In addition, PFS is considered to be the best surrogate marker of efficacy of a therapy (74), due to the factors that can confound OS results as described in the previous section. The combined benefit of PFS and maintenance in QoL was demonstrated via the TTD endpoint in the axitinib pivotal trial.

As highlighted in Section 6.10.1, AEs reported associated with axitinib treatment were generally mild or moderate in severity and clinically manageable; this was reflected in the lower discontinuation rate in the pivotal trial compared with sorafenib. As some treatment related adverse events can significantly affect patients QoL and daily functioning, the favourable AE profile of axitinib may provide an additional benefit for patients.

6.10.4 *Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the*

technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The evidence base for axitinib reflects the licensed indication and its anticipated use in clinical practice. In the pivotal trial, patients received axitinib at a starting dose of 5 mg BD with the option to titrate upwards to 7 mg and 10 mg BD or downwards to 3 mg or 2 mg BD, as indicated in the SPC (Section 10.1 Appendix 1). The patients enrolled in the pivotal trial were purely second-line patients only and the vast majority had received sunitinib or cytokines as their first-line treatment, in line with the licensed indication and reflecting the criteria that would be used to determine patient eligibility for axitinib treatment in clinical practice.

The patient population enrolled in the pivotal trial is considered to accurately reflect the UK patient population, as the majority of patients in each treatment arm were enrolled in centres in North America or Europe (76% of the axitinib arm and 74% of the sorafenib arm). Axitinib efficacy and tolerability has been demonstrated in a patient population refractory to the most widely used first line targeted therapy, sunitinib, and therefore, representative of UK clinical practice. In the Phase III trial eligible prior first-line treatments included all those licensed at the time of the trial design. Pazopanib a first-line treatment option currently available to UK patients was not licensed at the time of the phase III trial design. Patients could have had one of four prior treatments, sunitinib (54% n=389), or a cytokine (35% n=251), bevacuzimab + interferon alpha (IFN-α) (8% n=59) or prior temsirolimus (3% n=24).

7 Cost-effectiveness

Key points

- The present economic evaluation assessed the lifetime cost-effectiveness of axitinib versus best supportive care (BSC) in patients with advanced/mRCC after failure of prior treatment with sunitinib or a cytokine in the UK.
- A cost-effectiveness model was developed based on available RCT data from the AXIS study. It was necessary to supplement AXIS clinical data with comparative evidence from the TARGET trial, STC and RENCOMP studies to compare axitinib to BSC.
- Health outcomes were measured in terms of quality adjusted life years (QALYs) based on extrapolated overall survival (OS) and progression-free survival (PFS) estimates and EQ-5D utility values. Cost assessed included drug acquisition costs, routine medical management, and adverse event management.
- For the cytokine refractory population, the indirect comparison via the TARGET study was used as base case but is likely a conservative estimate due to confounding by crossover in the TARGET study.
- For the sunitinib refractory population, the STC was chosen as base case as it overcomes the key limitations of the evidence network (uncertainty in the incremental OS measurement from the AXIS study, and lack of direct evidence comparing sorafenib to BSC in a sunitinib refractory population. The RENCOMP analysis does not correct for confounding of OS in the AXIS study and so was retained as scenario analysis.
- The base case estimates for incremental cost-effectiveness ratios (ICERs) versus BSC in the cytokine and sunitinib refractory subgroups [redacted].
- Probabilistic sensitivity analysis demonstrated that the probability of axitinib being cost-effective versus BSC at a willingness to pay threshold of £50,000 was [redacted] in the base case sunitinib refractory analysis and [redacted] in the cytokine refractory analysis.
- As the absolute survival estimates for axitinib from the AXIS trial can be viewed as relatively robust, the key source of uncertainty in the model is the absolute survival estimate produced by the model for treatment with BSC. Within the everolimus STA a median BSC TKI-refractory survival of 8.9 months estimated, based on the RECORD-1 study and analyses to adjust for crossover. Published UK sources and the RENCOMP study report survival median sunitinib refractory BSC in the 4-6 month range. The base case BSC median OS estimate in this analysis is 8.3 months, and thus can can be viewed as a conservative analysis.
- Similarly to other first-line and second-line treatment for advanced/mRCC, axitinib fulfils the end of life criteria of providing a substantial life extension of greater than three months in a small patient population with a current life expectancy of less than

24 months.

Identification of studies

7.1 Published cost-effectiveness evaluations

7.1.1 ***Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision prob lem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, appendix 10.***

Please refer to Section 10.10 (Appendix 10) for full details of the systematic review

Description of identified studies

7.1.2 ***Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided.***

Please refer to Section 10.10 (Appendix 10) for full details of the systematic review

7.1.3 ***Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996 BMJ 313 (7052): 275–83), or Philips Z, et al. (2004 Health Technology Assessment 8: 36). For a suggested format based on Drummond and Jefferson (1996), please see Section 10.11, appendix 11.***

A quality assessment of each cost-effectiveness study is presented in Section 10.11 (Appendix 11).

7.2 De novo analysis

Patients

7.2.1 ***What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in Sections 1.4 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.***

An economic model was developed to assess the cost-effectiveness of axitinib versus best supportive care (BSC) in patients with advanced/mRCC after failure of prior treatment with sunitinib or a cytokine. As there is no second-line treatment option for

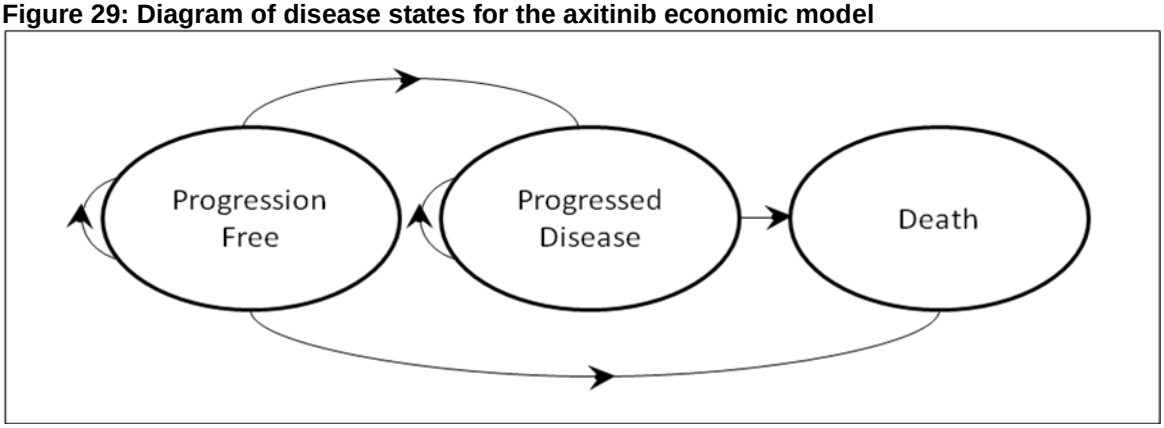
advanced/mRCC recommended by NICE, BSC was chosen as the relevant comparator, in keeping with the final appraisal scope.

The model examines the two distinct sub-populations of the AXIS trial, in keeping with the axitinib marketing authorisation: for treatment of advanced/mRCC after failure of prior treatment with sunitinib or a cytokine (see Section 10.1, Appendix 1).

Model structure

7.2.2 *Please provide a diagrammatical representation of the model you have chosen*

Figure 29: Diagram of disease states for the axitinib economic model



7.2.3 *Please justify the chosen structure in line with the clinical pathway of care identified in Section 2.5.*

The model structure is fully aligned with two of the primary objectives of treatment in advanced/mRCC; namely prolonging life and avoiding disease progression. This model structure and the health states utilised are typical of modelling in metastatic oncology and have been utilised in numerous NICE STAs and MTAs previously.

7.2.4 *Please define what the health states in the model are meant to capture.*

The progression free health state is designed to capture a patient‘s relatively high quality of life period prior to their disease progression. The PD state is designed to capture the relatively poor quality of life phase post disease progression and prior to death. These health states are those typically utilised in the modelling of metastatic oncology.

7.2.5 *How does the model structure capture the main aspects of the condition for patients and clinicians as identified in Section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to Section 2.1.*

The cost-effectiveness model was developed in Microsoft Excel® using a semi-Markov “area under the curve” structure in both a deterministic and probabilistic (Monte Carlo simulation) framework. The structure of the model has been chosen based on previously identified models of advanced/mRCC treatment and validated by UK clinician expert opinion (15, 29, 34, 76). It contains the three most relevant health states from a patient,

clinician and NHS perspective: progression free (PF), progressed disease (PD) and death (Figure 29).

- Progression free– during this stage it is assumed that patients' tumours are expected to be in a stable or responding state and not actively progressing. Patients in this stage are assumed to incur costs associated with active management, (including cost of drug for the axitinib arm, but not for the BSC arm) and costs associated with medical management of the condition and grade 3/4 adverse events. Patients also experience a higher utility weighting associated with non-progressing disease.
- Progressed disease – in this stage patients are assumed to have stopped treatment due to progression of disease and, in keeping with existing NICE guidance are expected to receive only best supportive care. Patients continue to incur costs associated with medical management and palliative care, and experience a lower utility weighting.
- Death – this is an absorbing health state.

In Figure 29, circles represent health states and arrows represent transition between states. At any point in time, a patient is assumed to be in one of the states. Patients move between states at the end of each four-week model cycle. This means, for example, that if a patient is in the PF health state, during the next cycle they can either die, move to the PD health state or remain in the PF health state. The health states of a cohort of patients are modelled at each discrete model cycle. All patients enter the model in the progression free health state, having progressed on a previous advanced/mRCC treatment. Patients remain in the progression free health state until they experience disease progression or die. Once patients enter the PD state, they remain there until death.

The model uses estimates of clinical effectiveness, costs and health related quality of life (HRQoL) estimates to model progression of disease and cost-effectiveness over time. The proportion of patients in each health state at each point in time is calculated directly from parametric survival function equations for the PF and PD states. A time horizon of lifetime (10 years) has been chosen in line with the life expectancy of the cohort and previously identified models of advanced/mRCC treatment. The impact of the selection of the time horizon on results is explored in sensitivity analysis.

This structure is regarded as appropriate for capturing the health effects, and complexities of natural history/disease progression in advanced/mRCC, and parallels the measurement time points from the pivotal AXIS study. In addition it is consistent with previous NICE appraisals in advanced/mRCC e.g. the model written by the Assessment Group for sunitinib, bevacizumab, sorafenib and temsirolimus for advanced/mRCC (130), and other advanced/metastatic solid-tumour cancers.

The analysis was conducted from an NHS and Personal Social Services perspective in England and Wales using 4 week model cycles, a lifetime horizon of 10 years, with 3.5% per annum discounting applied for cost and QALY benefits. Life years and QALYs gained were generated for the axitinib and BSC arms in order to estimate the incremental cost per QALY gained.

7.2.6 *Please provide a table containing the following information and any additional features of the model not previously reported.*

Table 33: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	Aligned with estimated life expectancy for the majority of cohort and previous advanced/mRCC economic models. Only 3% of patients in the model are alive after 10 years. See section 7.3.2.1 for description of long-term survival estimates in model.	(131)
Cycle length	4 weeks	Aligned with trial measurement periods, drug dispensation and clinical follow-up visits	(131)
Half-cycle correction	Yes	NICE reference case	(131)
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case	(131)
Discount of 3.5% for utilities and costs	Yes	NICE reference case	(131)
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	(131)

Abbreviations: mRCC, metastatic renal cell carcinoma; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PSS, Personal Social Services; QALYs, quality-adjusted life years.

Technology

7.2.7 *Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in Sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?*

The sunitinib-refractory and cytokine-refractory sub-populations form the main focus of this submission in line with the marketing authorisation of axitinib (see Section 10.1; Appendix 1). Axitinib is indicated for the treatment of adult patients with advanced/mRCC after failure of prior treatment with sunitinib or a cytokine. The model examines these two subgroups in separate analyses as cytokine refractory patients are considered by many clinicians to comprise a different subgroup of patients compared with those who are sunitinib refractory.

7.2.8 ***Please note that the following question refers to clinical continuation rules and not patient access schemes. If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.***

No additional treatment continuation rule has been assumed in the model, beyond the requirements of the marketing authorisation. The model assumes axitinib therapy will be delivered until progression, death (if occurring prior to disease progression), or withdrawal during adverse events, in line with the SPC (see section 10.1; Appendix 1) and expected UK clinical practice.

7.3 Clinical parameters and variables

7.3.1 ***Please demonstrate how the clinical data were implemented into the model.***

The clinical effectiveness data utilised by the economic model is outlined below. The section begins by describing the approach taken to incorporate the clinical data for axitinib treatment in the two relevant subgroups assessed in the model – cytokine refractory and sunitinib refractory. It then outlines the approach taken to model the comparator treatment (BSC) for the two subgroups, including an overview of the evidence network, any limitations discussed, and the approaches explored to model BSC.

7.3.1.1 Axitinib arm

The clinical trial efficacy endpoints included in the model were PFS and OS. The specific definitions of PFS and OS included in the model were:

- **PFS** defined as the time from date of randomisation to date of the first documentation of objective tumour progression or death due to any cause (as assessed by the Independent review committee; IRC).
- **OS** defined as the time from date of randomisation to date of death due to any cause.

For patients alive at the time of the analysis, the OS time was censored on the last date they were known to be alive. Tumour response rates were assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria (version 1.0).

Section 7.3.2 outlines the methodology used to incorporate the axitinib clinical data for PFS and OS into the economic model.

7.3.1.2 Comparison with BSC

As the AXIS trial included an active comparator (sorafenib, which was the only licensed second-line treatment for advanced/mRCC at the time of commencement of the trial), and NICE does not recommend any second-line treatement for advanced/mRCC, it was necessary to utilise statistical analyses to model BSC OS and PFS. However, when attempting to create an axitinib vs. BSC indirect comparison, a number of limitations in the evidence network were identified which impacted the methodological approach taken

for the comparison with BSC. Section 6.7.2 outlines these limitations and describes the methodologies applied to overcome them.

Given these limitations identified in the evidence network, it was necessary to apply a number of methodological approaches to attempt to create a valid and unbiased comparison between axitinib and BSC for the two relevant model populations, the following section outlines this approach, beginning with the cytokine refractory population and concluding with the sunitinib refractory population.

7.3.1.3 Prior cytokine population

Despite the limitations in the evidence network of cytokine refractory RCTs, the indirect comparison via the TARGET study was determined to be the best approach available to estimate BSC survival in the cytokine refractory population. The methodology for this indirect comparison is detailed in Section 6.7. Briefly, an indirect comparison was performed between the cytokine refractory population in the AXIS study and the TARGET study to generate an indirect axitinib-BSC hazard ratios for both PFS and OS. The results of the indirect comparison are detailed in Section 6.7.6. Full details of the method of selection used and evidence sources are available in Section 6.7.5.

To incorporate the BSC efficacy data in the economic model, adjusted BSC curves were created by applying the hazard ratios from the indirect comparison to the survival functions used to model the axitinib cytokine refractory curves in the model base case. This methodology implies an assumption of proportional hazards between the two treatment groups. The assumption of proportional hazard implies that for the two treatment groups considered within the model, the hazard of the event for an individual in one group at any time point is proportional to the hazard of a similar individual in the other group—the treatment effect is measured as a hazard ratio (132). While this assumption is a potential source of structural uncertainty, it is necessary in order to incorporate a hazard ratio from an indirect comparison and is commonly made in oncology economic modelling. Proportional hazard assumptions are commonly made in NICE appraisals, and have been accepted previously in advanced/mRCC (29, 34, 76). The NICE DSU Technical Support Document on Extrapolation notes that the use of proportional hazard modelling was evident in 19 of the 32 technology appraisals that involved extrapolation of survival data, and is often used when multiple comparators were included in the evaluation, and where patient-level data were not available for all comparators, as is the case for this model (132).

7.3.1.4 Sunitinib refractory population

In contrast to the cytokine refractory population, where the TARGET trial allows for a comparison between axitinib and BSC (despite the limitations of crossover discussed in Section 6.7.2), no comparable RCT or observational data exists comparing sorafenib with axitinib in a sunitinib refractory population. Thus, several approaches were explored to determine a way to compare the sunitinib refractory AXIS subgroup and a sunitinib refractory BSC population.

First, a simulated treatment comparison (STC) approach was used to create a “mock-randomised” comparison between the AXIS prior sunitinib arm and the prior-tyrosine kinase inhibitor (TKI) BSC arm of the RECORD-1 study. Second, a retrospective

database analysis was carried out to compare the efficacy of sorafenib and BSC in a real-world population.

Method 1: Simulated treatment comparison

The following section (7.3.2) includes a further description of the methodology, results and discussion of the simulated treatment comparison as described in Section 6.7.11, as well as an overview of the approach taken to incorporate the results in the economic model.

Method 2: Real world data – RENCOMP

The second approach considered in the economic model, was to use a non-RCT evidence source to determine the relative efficacy of sorafenib and BSC in a sunitinib refractory population, thereby replacing the missing comparison in the evidence network and allowing a valid axitinib-BSC prior sunitinib indirect comparison to be made. As the systematic review reported in Section 6.1 indicates, no RCT or non-RCT evidence was identified comparing sorafenib with BSC in a sunitinib-refractory population. Thus, a *de-novo* analysis was carried out using a national claims database (RENCOMP) to estimate the incremental OS benefit of sorafenib vs BSC in a retrospective, non-interventional study framework.This is described in detail in Section 6.7.12.

Briefly, the approach taken to determine the relative treatment effect, and incorporate it into the economic analysis, was as follows:

- To correct for possible confounders (prognostic patient characteristics that may be different between the two treatment arms) a multivariate Cox proportional regression analysis was performed to generate adjusted OS hazard ratios for sorafenib vs. BSC.
- The RENCOMP prior sunitinib-sorafenib vs prior sunitinib-BSC hazard ratio was then included in an indirect comparison alongside the AXIS sunitinib refractory hazard ratio between axitinib and sorafenib to generate hazard ratios between axitinib and BSC in a sunitinib refractory population.
- The axitinib-BSC hazard ratio was then applied to the parametric survival functions for the axitinib data to estimate BSC OS in the economic model.

The results of the analysis and the method of incorporation into the economic model, as well as a discussion of the inherent assumptions, limitations and advantages of this approach, are described in Section 7.3.2.

7.3.2 *Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.*

This section describes the results of the various methods considered in Section 7.3.1 to model both axitinib and comparator data for the cytokine refractory and sunitinib refractory subgroups. It begins by describing the results of the parametric survival analysis carried out to incorporate the axitinib treatment arm in the economic model for the cytokine refractory and sunitinib refractory populations. Next, the results of the indirect comparison methodology used to model BSC in the cytokine refractory population are discussed. Finally, the results of the two methodologies used to model

BSC in the sunitinib refractory population are discussed, beginning with the STC and concluding with the RENCOMP study.

7.3.2.1 Axitinib treatment arm – extrapolation approach

Methodology

To model axitinib efficacy data, PFS and OS were incorporated into the economic model using parametric survival curves to determine the proportion of patients in the progression-free, progressed disease and death health states. The framework used follows the approach recommended in the NICE Decision Support Unit technical support document number 14 (132).

Patient level data on PFS and OS were based on the most recent June 2011 and November 1, 2011 data cut-off respectively (46, 63).

Patient-level data were analysed using, exponential, Weibull, Gompertz, lognormal and loglogistic distributions (using Stata 10.0). Data were fitted to the clinical survival data for the axitinib treatment arm separately for the cytokine refractory and sunitinib refractory subgroups (Sorafenib data were not included as it is not a relevant comparator for the model). Of the five distributions tested, the three judged the best fits were included in the model, with the base case representing the most plausible survival estimate, and the two scenario analyses representing alternate options.

To determine the best model fit, the following criteria were considered, with the most appropriate model identified based on a combination of these:

- **AIC/BIC** - Model fits were evaluated using Akaike's information Criteria (AIC) and Bayesian Information Criteria (BIC) statistics. Lower AIC/BIC figures are indicative of a better statistical fit of the survival function of the Kaplan-Meier data
- **Visual Inspection** - Visual inspection was carried out by plotting the projected survival curves overlaid with the Kaplan-Meier survival functions. Estimates were evaluated based on the goodness-of-fit of the parametric survival curve to the Kaplan-Meier curve during the trial period, and the clinical plausibility of the proportion of patients estimated to be surviving at the tails of the curve. Fits were first assessed by the economic modelling team and validated using clinical input from UK expert clinical opinion following the approach outlined in section 7.5.
- **Anchoring** – Wherever possible, extrapolation estimates were validated through comparison with more mature external data sources.

Results

Prior cytokine - OS

For the cytokine refractory OS data, the Weibull model was chosen for the base case, with log logistic and Gompertz explored in scenario analyses. Exponential and lognormal models were not incorporated int the model due to poor fits but are detailed in appendix 18.

The loglogistic model provided a good fit in statistical terms (AIC and BIC). However, based on visual inspection and anchoring, the Weibull model was considered to be the most plausible. As Figure 30 shows, the Weibull model provides an intermediate survival

estimate between loglogistic and Gompertz. Furthermore, high-quality anchoring data was available from an axitinib Phase II study in a cytokine refractory population (67). The 5-year survival rate from this study (20.6%, 95% CI 10.9-32.4) corresponded almost exactly to the 5-year Weibull prediction (20.8%), with the Gompertz and loglogistic estimates (9.9% and 29.8% respectively), corresponding closely to the upper and lower confidence intervals.

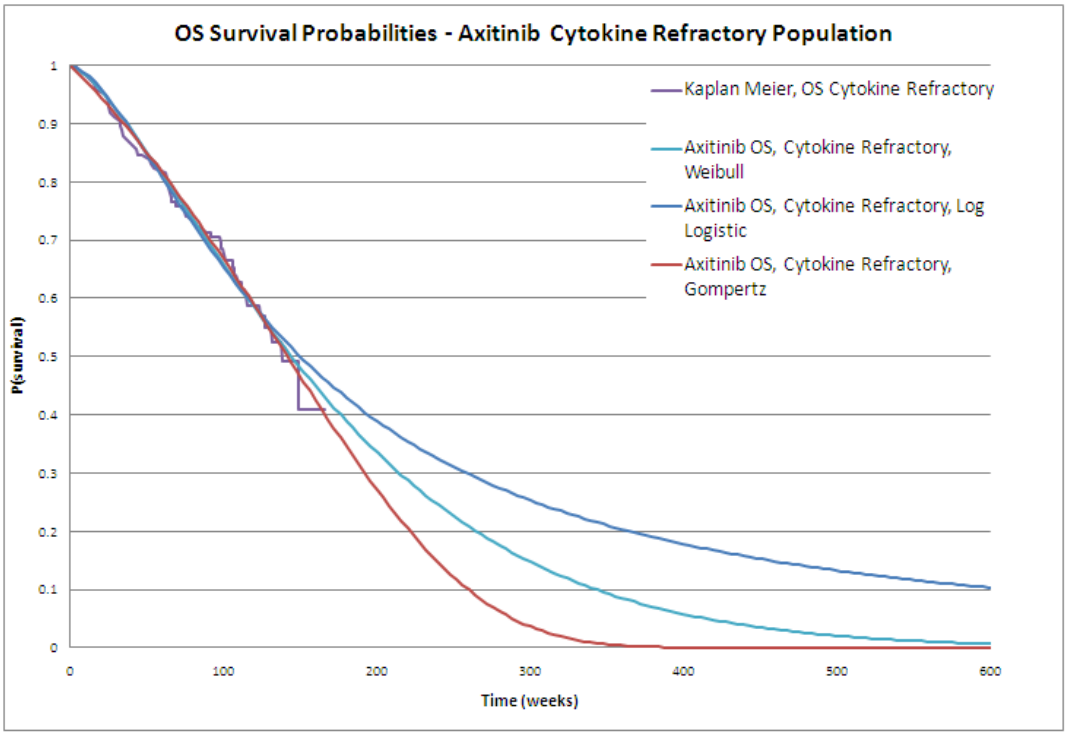
Additionally, the Weibull model allows for the incorporation of a hazard ratio to model the BSC arm, in keeping with the indirect comparison framework used for the cytokine refractory population (as described in Section 7.3.1 and later in Section 7.3.2). While the loglogistic model provided the best fit in statistical terms (AIC and BIC), it did not allow for the application of the indirect comparison hazard ratio as it is an accelerated failure time model. Therefore, the loglogistic model was not chosen as base case where the application of a proportional hazard was required. The Gompertz model was retained and explored in a scenario analysis.

Table 34 shows the model fit of the survival functions; AIC and BIC statistics for each of the evaluated model fits are available in Section 10.19 (Appendix 18).

Table 34: Model shapes for OS in the cytokine-refractory population

Model	Degrees of freedom	AIC	BIC
Weibull	2	250.1823	255.8548
Gompertz	2	251.2509	256.9235
Loglogistic	2	250.7399	256.4124

Figure 30: OS Survival probabilities – Axitinib cytokine refractory population



Prior cytokine - PFS

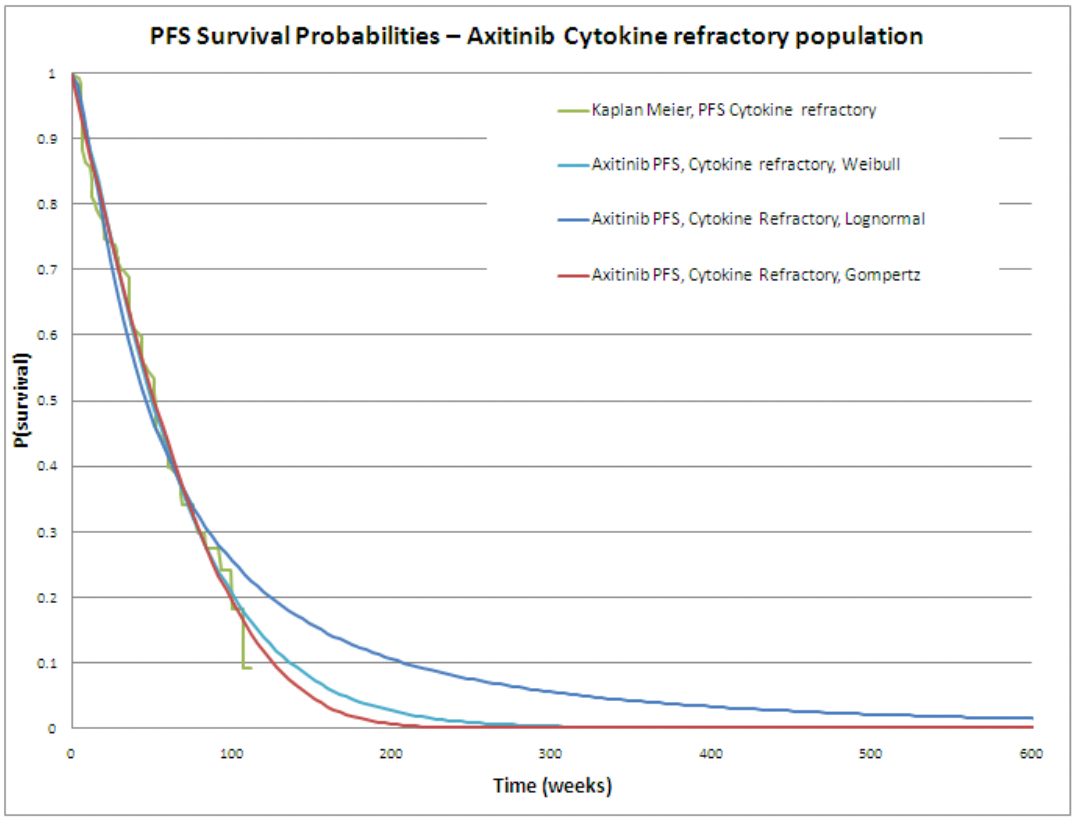
For the cytokine refractory PFS data, the Weibull curve was again chosen as the base case, with Gompertz and lognormal retained in the model for scenario analyses. Exponential and loglogistic models were not included in the model due to poor fits but are detailed in appendix 18.

Due to the higher proportion of patients having reached the PFS endpoint during the follow-up period than in the OS data, there was less variation between the different models. Similarly to the OS data, the lognormal model provided the best fit in terms of AIC-BIC and fit to the trial portion of the Kaplan Meier curve. However, the lognormal model predicted a substantially higher proportion of non-progressed patients at 10 years than the other two models, which was felt to be clinically implausible by the experts consulted (Table 35).

Table 35: Model shapes for PFS in the cytokine-refractory population

Model	Degrees of freedom	AIC	BIC
Weibull	2	293.5021	299.1747
Gompertz	2	294.2111	299.8837
Lognormal	2	293.7307	299.4033

Figure 31: PFS Survival probabilities – Axitinib cytokine refractory population



Prior sunitinib - OS

For the sunitinib refractory OS data, a lognormal model was chosen as the base case, with Weibull and Gompertz examined in scenario analyses (Table 36). Exponential and

loglogistic models were excluded from the model based on poor fits but are again fully detailed in appendix 18.

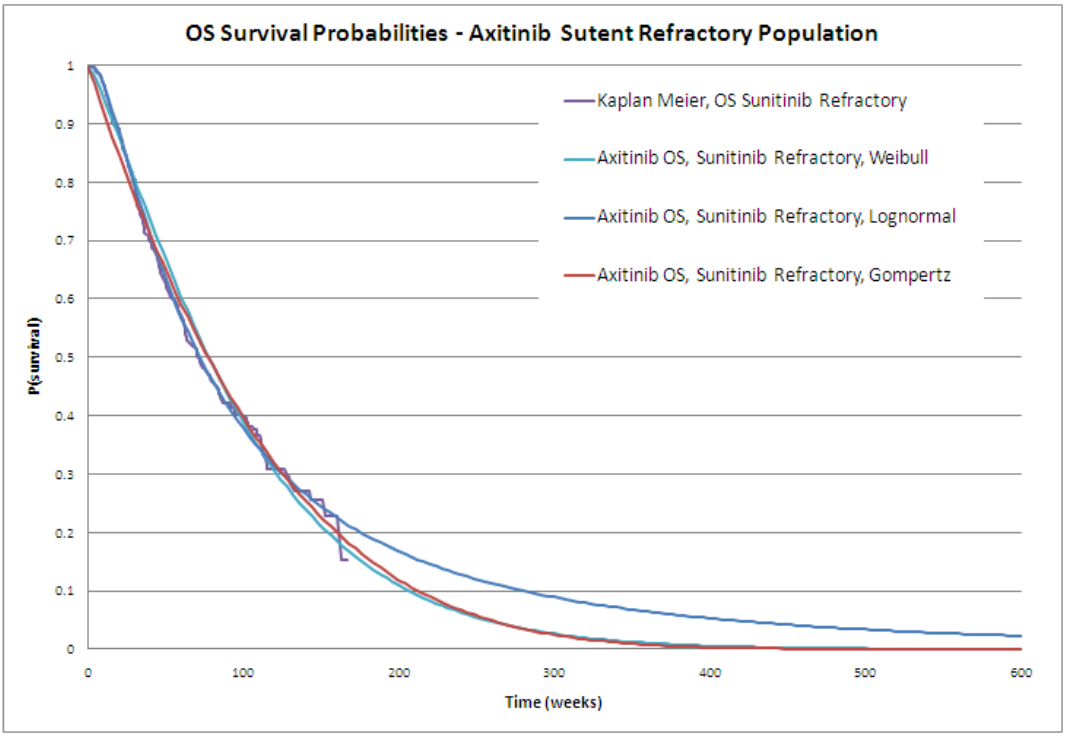
In contrast to the cytokine refractory population, where a larger proportion of patients remained alive at the end of the trial follow up period (likely due to the less progressed nature of disease for the cytokine refractory patients), the sunitinib refractory dataset was more complete and allowed for more accurate OS extrapolation. Of the model fits evaluated, the lognormal provided the most accurate fit to the data and AIC/BIC. In this case the lognormal, while producing the longer survival estimates than the Weibull and Gompertz models, was considered a more clinically plausible survival estimate by the experts consulted (predicting approximately 3% survival at 10 years). This “tail” is consistent with the heterogeneous nature of advanced/mRCC whereby a low proportion of treated patients can generally be expected to survive for long periods of time.

While no long term follow-up data is available for axitinib patients in a sunitinib-refractory population, the survival proportion predicted by the lognormal model is similar and therefore plausible, to the results of the cytokine refractory 5-year follow up data from the axitinib Phase II trial (67). Moreover, as demonstrated in Figure 32, the sunitinib-refractory Kaplan Meier curve appears to demonstrate a non-monotonic hazard, with the curve appearing more concave in the middle portion. The Gompertz and Weibull curve appear to over-predict survival in the middle part of the curve, with the lognormal (allowing for upwards and downwards variations in the rate of change of the survival function over time) tracks the curve better for the entire period. Additionally, since the base-case STC analysis does not require the application of a hazard ratio, the lognormal method was retained as the base case, with Weibull examined in scenario analysis.

Table 36: Model shapes for OS in the sunitinib-refractory population

Model	Degrees of freedom	AIC	BIC
Weibull	2	506.633	513.1687
Gompertz	2	512.2575	518.7933
Lognormal	2	496.1517	502.6874

Figure 32: OS Survival probabilities – Axitinib sunitinib refractory population



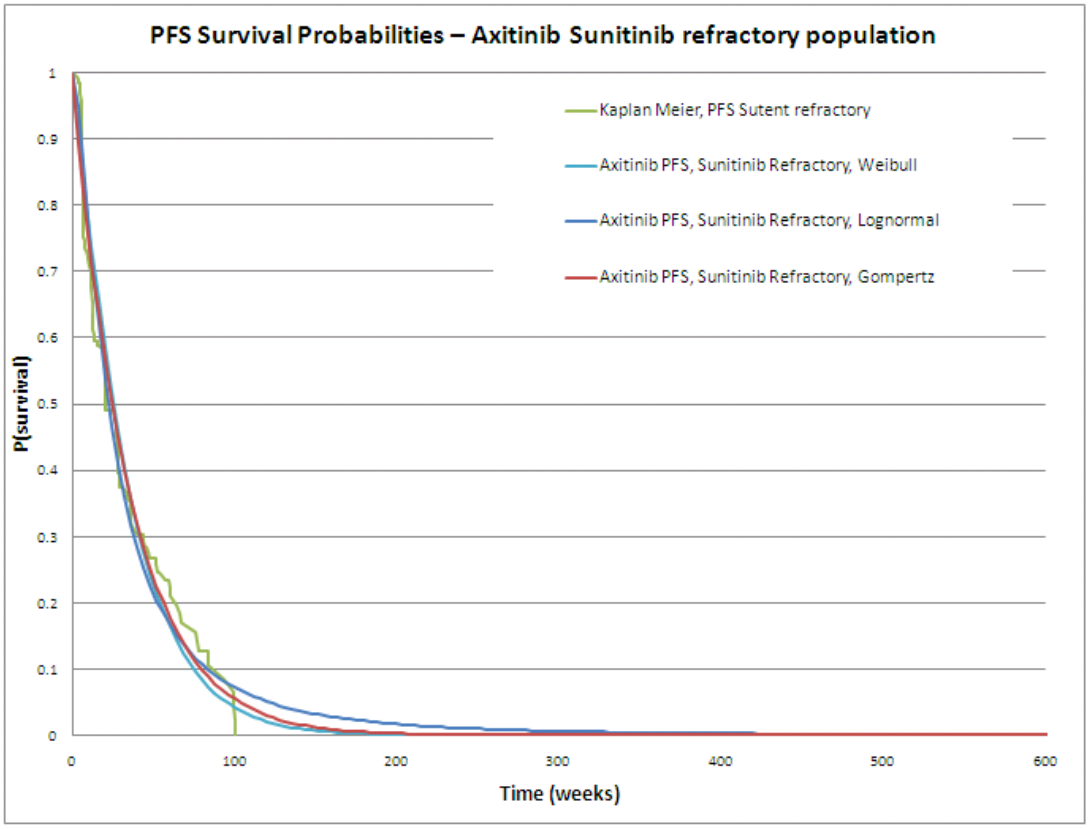
Prior sunitinib - PFS

For the sunitinib refractory PFS data, Weibull was chosen as the base case, with lognormal and Gompertz curves also included in the model, and exponential and loglogistic models excluded but detailed in appendix 18. For these data, the three model shapes evaluated provided highly similar fits, with the least variation in predicted survival times of the curves evaluated, likely due to the fact that the survival data was over 90% complete at the cut-off point (Table 37). The lognormal curve again had the best fit in terms of AIC and BIC. However, the it resulted in a survival estimate at the tail end of the curve which was considered clinically implausible, so the Weibull model, which produced an intermediate PFS estimate between lognormal and Gompertz, was chosen as base case. Finally, while no anchoring data was available, the data was highly complete and so anchoring would be of limited usefulness.

Table 37: Model shapes for PFS in the sunitinib-refractory population

Model	Degrees of freedom	AIC	BIC
Weibull	2	496.7759	503.3116
Gompertz	2	498.9336	505.4693
Lognormal	2	475.3779	481.9136

Figure 33: PFS survival probabilities – Axitinib sunitinib refractory population



Abbreviations: PFS, progression-free sur cytokine refractory vival.

7.3.2.2 BSC comparison – cytokine refractory population

As discussed in Section 7.3.1, to model the BSC arm for the cytokine refractory population, the indirect comparison between axitinib and BSC via the TARGET crossover-censored hazard ratio was identified as the most valid methodological approach. As the TARGET trial examined a similar population to the AXIS cytokine refractory subgroup and reported a RECIST-defined, unbiased PFS hazard ratio, the PFS indirect comparison can be considered an accurate estimate. Although the TARGET OS is likely confounded by the lack of an accepted methodology to adjust for crossover, the indirect comparison nonetheless presented the best available source for the BSC comparison. However, due to the confounding present in the study measurement, the incremental OS benefit for axitinib in this sub-population can likely be considered as an underestimate.

The results of the indirect comparison (discussed in Section 6.7) are displayed in Table 38.

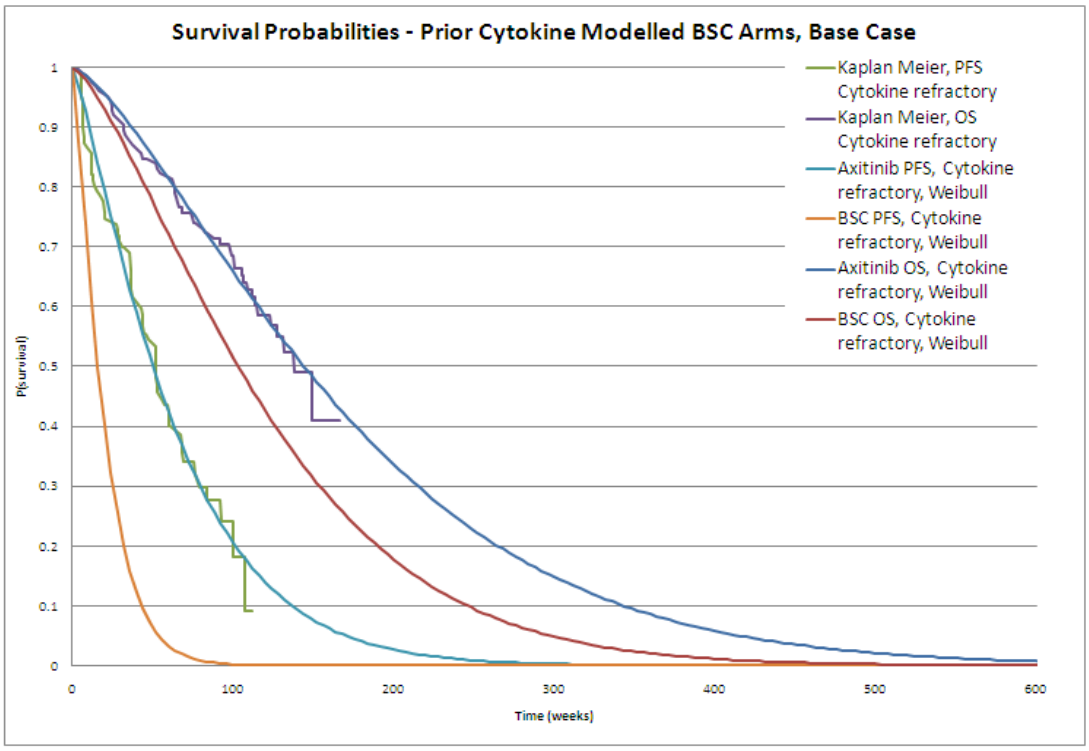
Table 38: Axitinib-BSC cytokine refractory hazard ratios used in the economic model

	HR (95% CI): Axitinib vs BSC)
PFS	0.251 (0.165-0.379)
OS	0.63 (0.41-0.99)

Abbreviations: BSC, best supportive care; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

The modelled BSC curves are displayed in Figure 34. Appendix 18 (Section 10.19) contains details of the mathematical approach used to apply the hazard ratios to the parametric survival equations.

Figure 34: Survival probabilities – Prior cytokine modelled BSC arms, base case



Abbreviations: BSC, best supportive care; OS, overall survival; PFS, progression-free survival.

7.3.2.3 BSC comparison – sunitinib refractory population

As previously mentioned, the key limitations of the evidence network for making a comparison between axitinib and BSC in the sunitinib refractory patient population are the uncertainty in the incremental OS measurement from the AXIS study, the confounding of OS data in the TARGET study due to cross-over and the lack of evidence comparing sorafenib to BSC in a prior sunitinib population. Given these three limitations, both the RENCOMP and STC methodologies were examined in the modelling approach.The RENCOMP analysis replaces the gap in the evidence network by providing clinical data in a prior sunitinib patient population who received second-line sorafenib or BSC. This analysis corrects two of these shortcomings, but not the other. The STC, however, overcomes all these limitations. The STC allows a direct link to be made between the AXIS axitinib arm and the RECORD-1 BSC arm, removing the requirement to correct for confounding in the AXIS OS relationship. For this reason, the STC has been chosen as the base case approach for the sunitinib refractory population, with the RENCOMP retained and explored in scenario analysis. These analyses are described in detail in Sections 6.7.11 and 6.7.12

Method 1: Simulated treatment comparison

The methodology and results of the STC are described in Section 6.7.11. Please refer to Figure 21 to Figure 26 for the results.

Method 2: RENCOMP Indirect comparison

The methodology and results of the RENCOMP analysis and subsequent indirect comparison are described in Section 6.7.12.

Incorporation of RENCOMP hazard ratios into economic model

To address the limitation in the evidence network due to the lack of a sorafenib vs. BSC RCT data in a sunitinib refractory population, an indirect comparison was conducted by incorporating the RENCOMP hazard ratio into a meta-analysis, using the sunitinib refractory OS hazard ratio from the AXIS study (0.997, 95% CI 0.782,1.27) to generate an axitinib-BSC OS hazard ratio. The methodology for the comparison follows the same approach described in Section 7.3.2.2 for the cytokine refractory population. Calculated hazard ratios are displayed in Table 39, and full results are included in Appendix 18 (Section 10.19)

Table 39: Axitinib-BSC sunitinib refractory (via RENCOMP) OS hazard ratios

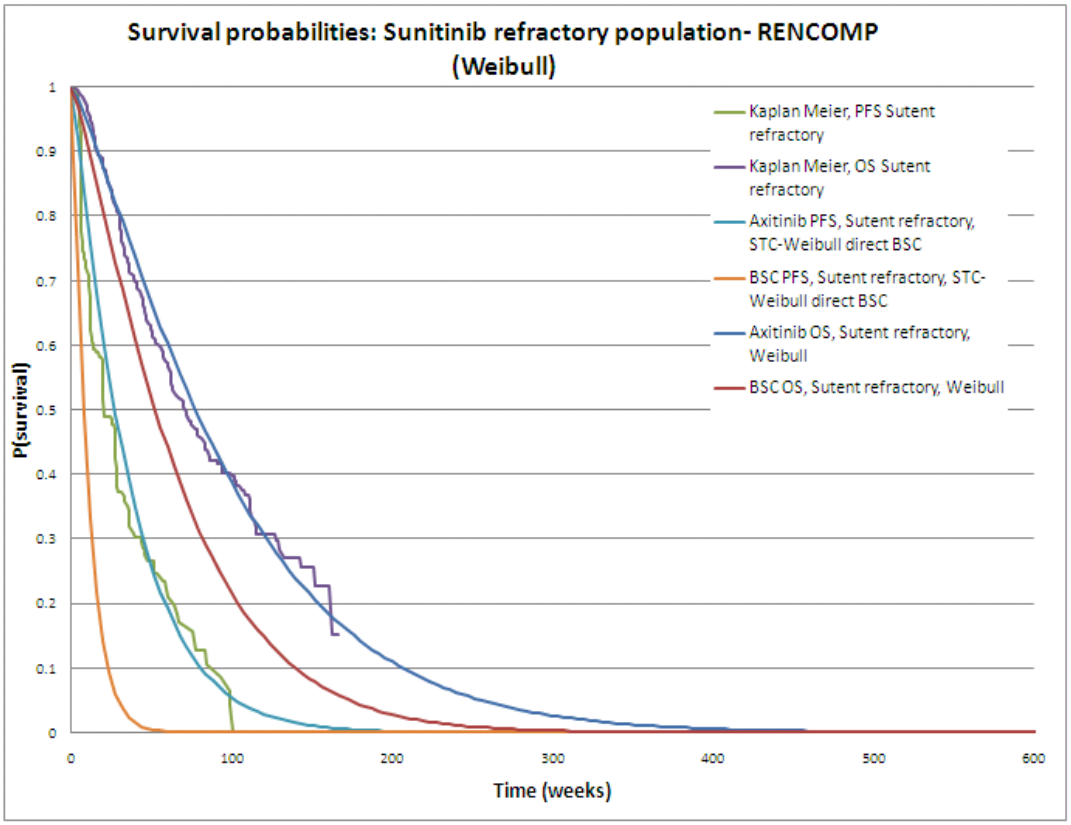
	OS HR (95% CI)
Axi-BSC RENCOMP HR	0.619 (0.384-0.997)

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

To incorporate the hazard ratio into the economic model, parametric survival curves for best supportive care were generated by applying the OS hazard ratio to the axitinib parametric survival function, as described in the cytokine refractory section using the approach outlined in Appendix 18 (Section 10.19).

The following graph illustrates the modelled BSC survival function using the RENCOMP hazard ratio when applied to the Weibull model. Despite the better fit provided by the lognormal model, the Weibull was used as the base case for the RENCOMP data, as accelerated failure time models like the lognormal and loglogistic assume a constant proportional hazard and thus do not allow for the application of a hazard ratio into the functional form. However, despite this shortcoming, application of the hazard ratio to the loglogistic model was explored in scenario analysis using the functional approach detailed in appendix 17 (Section 10.16). While this approach has technical limitations, it allows for the application of the hazard ratio to the loglogistic survival function identified as base case and demonstrates the application of this hazard ratio to the more plausible survival trend from the base case.

Figure 35: Survival probabilities – RENCOMP (Weibull)



Abbreviations: BSC, best supportive care; OS, overall survival; PFS, progression-free survival.

Discussion

The use of RENCOMP data corrects one of the main limitations in the evidence network: the lack of sorafenib-BSC data in the sunitinib refractory population. However, it should be noted that this analysis does not correct for potential confounding in the OS estimate between the axitinib and sorafenib treatment arms in the AXIS study. As discussed in Section 7.3.1, the measurement of OS in the AXIS study is subject to a number of substantial limitations including the inherent difficulty of demonstrating incremental OS benefit in an oncology trial with long post progression survival, the potential masking of OS benefit due to the use of an active comparator, and confounding by the administration of non-randomised post-study treatment.

Thus, the indirect comparison via RENCOMP can potentially be viewed as a conservative estimate which likely underestimates the true incremental overall survival axitinib versus BSC in a sunitinib refractory population.

7.3.3 *Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.*

Examination of survival curves functions from this and other oncology RCTs indicates that transition probabilities are likely to vary over the course of the disease. The parametric survival method used to model transition probabilities allows for flexibility in the rate of change of the survival functions over time. The alternate scenario analyses

examined in the model allow for different assumptions about the variation of transition probabilities over time to be examined.

7.3.4 *Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?*

Intermediate outcome measures were not considered in this appraisal.

7.3.5 *If clinical experts assessed the applicability of values available or estimated any values, please provide the details.*

Expert opinion was solicited to test and verify all key model inputs, including:

- Choice of extrapolation method for OS and PFS curves;
- Methodology and results of the indirect comparison and STC approaches;
- Resource utilisation estimates for routine medical management and management of adverse events; and
- Utility estimates.

In all cases, assumptions were first made in a manner consistent with published literature and previous NICE appraisals wherever possible. Input was sought from one clinical expert and one health economic expert. Assumptions were presented in face-to-face meetings as well as telephone and email discussions arranged on an ad-hoc basis.

The clinical expert consulted was chosen based on expertise as a consultant oncologist specialising in treatment of advanced/mRCC in the UK setting, experience with previous HTA appraisals for advanced/mRCC, and availability. The economic expert consulted was chosen based on general academic and professional qualifications as a health economist with experience in economic evaluation of health technologies in a UK setting, experience with previous NICE appraisals in advanced/mRCC, and availability.

In addition, further input was sought during an advisory board with five UK clinicians to further validate the Axitinib model arm extrapolations, as well as the STC and RENCOMP comparisons. All attendees of the session were consultant oncologists with significant experience in advanced/mRCC treatment. Attendees were chosen based on expertise, geographical representation, and availability.

Summary of selected values

7.3.6 *Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table.*

A list of all variables used in the economic analysis is provided in Table 40.

Table 40: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Utilities	Utility	SD/SE (beta)	Reference

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Base Case			
Progression Free	0.692	SD=0.275	7.4.9
Progressed Disease	0.610	SD =0.316	
Sensitivity Analysis			
Progression Free	0.758	SE = 0.03	7.4.9
Progressed Disease	0.683	SE = 0.04	
Cost	Cost (£)	SE (gamma)	Reference
Treatment			
Cost of axitinib	£3,517/28 days	n/a	7.5.5
Dosing intensity (base case)	102.00%	35.2%	
Dosing intensity (real world estimate)	80%	n/a	
Resource Utilisation			
Oncologist visit	£120.00	£22	7.5.6
GP visit (17.2 mins)	£53.00	£7.00	
GP visit (11.7 mins)	£36.00	£5.00	
District nurse visit	£38.00	£5.00	
CT Scan	£160.00	£20.00	
Full Blood Count	£3.36	£0.43	
Specialist Nurse visit	£84.00	£11.00	
Morphine sulphate	£5.00/day	£0.64	
Cost of death	£3923.00		
AE Management			

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Grade 3/4 diarrhoea	£272.00	SE = £35.00 (gamma)	7.5.7
Grade 3/4 anaemia	£1958.00	SE = £250.00 (gamma)	
Grade 3/4 hypertension	£276.00	SE = £35.00 (gamma)	
Hazard Ratios	HR	95% CI (lognormal)	Reference
Prior cytokine			
PFS, Axi vs. BSC via TARGET OS, Axi vs. BSC via TARGET crossover-censored	0.251 0.63	0.165 - 0.379 0.41 - 0.99	7.3.2
Prior sunitinib			
OS, Axi vs BSC via RENCOMP model	0.619	0.384 - 0.997	7.3.2
Survival Function Parameters	Value	Covariance Matrix	Reference
Axitinib cytokine refractory – PFS			
Weibull – Axitinib Parameter 1 = λ Parameter 2 = γ	[redacted]	**ln(λ)** / **lnγ** **ln(λ)** [redacted] **ln(gamma) lnγ** [redacted]	7.3.2
Lognormal – Axitinib Parameter 1= mean μ Parameter 2= lnσ	[redacted]	**Const** / **ln (sig)** **Const** [redacted] **ln (sig)** [redacted]	
Gompertz – Axitinib Parameter 1 = const Parameter 2 = γ	[redacted]	**Const** / **γ** **Const** [redacted] **gamma** [redacted]	
Axitinib cytokine refractory – OS			
Weibull Parameter 1 = λ Parameter 2 = γ	[redacted]	**ln(λ)** / **lnγ** **ln(λ)** [redacted] **ln(gamma) lnγ** [redacted]	7.3.2

Variable	Value	Measurement of uncertainty and distribution			Reference to section in submission
Loglogistic Parameter 1= λ Parameter 2= lnγ	[redacted]		**Const**	**ln_gam**	
		Const	[redacted]	[redacted]	
		ln_gam	[redacted]	[redacted]	
Gompertz Parameter 1 = const Parameter 2 = γ	[redacted]		**Const**	γ	
		Const	[redacted]	[redacted]	
		gamma	[redacted]	[redacted]	
Axitinib sunitinib refractory – PFS					
Weibull Parameter 1 = λ Parameter 2 = γ	[redacted]		**ln(λ)**	**lnγ**	7.3.2
		ln(λ)	[redacted]	[redacted]	
		ln(gamma) lnγ	[redacted]	[redacted]	
Lognormal Parameter 1 = mean μ Parameter 2 = S= lnσ	[redacted]		**Const**	**ln (sig)**	
		Const	[redacted]	[redacted]	
		ln (sig)	[redacted]	[redacted]	
Gompertz Parameter 1 = const Parameter 2 = γ	[redacted]		**Const**	γ	
		Const	[redacted]	[redacted]	
		gamma	[redacted]	[redacted]	
STC Adjustment Factors – PFS					
Weibull via sunitinib refractory via BSC	[redacted]				6.7.11
Lognormal via sunitinib refractory via BSC	[redacted]				
Weibull via sunitinib refractory via everolimus	[redacted]				
Axitinib sunitinib refractory – OS					
Weibull Parameter 1 = λ Parameter 2 = γ	[redacted]		**ln(λ)**	**lnγ**	7.3.2
		ln(λ)	[redacted]	[redacted]	
		ln(gamma) lnγ	[redacted]	[redacted]	
Lognormal Parameter 1 =	[redacted]		**ln(λ)**	γ	
		Const	[redacted]	[redacted]	

Variable	Value	Measurement of uncertainty and distribution			Reference to section in submission
mean μ Parameter 2= S= lnσ	[redacted]	**ln (sig)**	[redacted]	[redacted]	
Gompertz Parameter 1 = const Parameter 2 = γ	[redacted]		**ln(λ)**	γ	
		Const	[redacted]	[redacted]	
		gamma	[redacted]	[redacted]	
STC Adjustment Factors					
Weibull via sunitinib refractory via BSC	[redacted]				6.7.11
Lognormal via sunitinib refractory via BSC	[redacted]				
Weibull via sunitinib refractory via everolimus	[redacted]				

Abbreviations: AE, adverse event; BSC, best supportive care; CI, confidence interval; CT, computed tomography; GP, general practitioner; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparison.

7.3.7 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.*

Please refer to Sections 7.3.1 and 7.3.2 for discussion of the methods used to extrapolate clinical data.

7.3.8 *Provide a list of all assumptions in the de novo economic model and a justification for each assumption.*

Table 41 provides a brief overview of the main structural assumptions made by the economic model, and a summary of the justification for the decision. Please refer to the referenced section for a full overview of the assumptions in the context where they are discussed.

Table 41: Key model assumptions

Assumption	Justification	Reference to section:
Patients assumed to remain on axitinib until progression or	The model assumes axitinib therapy will be delivered until progression, death (if occurring	7.2.5

Assumption	Justification	Reference to section:
discontinuation due to adverse events	prior to disease progression), or discontinuation due to AEs, in line with the SPC, AXIS study results and expected UK clinical practice,	
Proportional hazard assumed for between axitinib and BSC treatment arms for all model cases (STC and indirect comparison-based approaches)	The assumption of proportional hazard assumption is required to create modelled BSC arm using either hazard ratio from indirect comparison or median survival time in STC. It is commonly made in oncology economic modelling and frequently applied in NICE appraisals.	7.3.1.3
Comparability between RECORD-1 and AXIS trials	In order to carry out the STC analysis with the RECORD-1 study it was necessary to assume comparability between AXIS and RECORD-1 patients. While the STC approach corrects for differences in observed covariates, two main sources of potential heterogeneity between the trials were identified which could not be corrected for: Differences in number of previous therapies between the AXIS and RECORD-1 studies, and inclusion of patients in the RECORD-1 study whom discontinued previous VEGF-TKI therapy due to intolerance.	7.3.1.3
Comparison of AXIS with either ITT BSC population or RPSFT-HR-adjusted prior sunitinib arm in RECORD-1	Since survival estimates for the prior sunitinib BSC only population have not been reported for the RECORD-1 study, two data sources were examined for the comparison, each necessitating different assumptions: Comparison with the ITT RPSFT-adjusted BSC population, and comparison with the prior sunitinib everolimus arm with the RPSFT hazard ratio applied to create a modelled BSC arm. The first approach assumes that prior sunitinib patients can be viewed as equivalent to those receiving other treatments. The second assumes that the RPSFT HR is constant between the RECORD-1 ITT population and the prior sunitinib population. As neither approach appeared inherently more supportable, the most conservative result (comparison via RECORD-1 ITT BSC arm) was chosen.	7.3.1.3, 7.3.2.3
No unobserved covariates	Both STC and RENCOMP analysis require the use of non-RCT data. While both approaches use statistical methodologies to adjust for observed imbalances in covariates associated with PFS and OS, these methodologies cannot account for any unobserved sources of confounding which would typically be accounted for due to randomisation of patients between trial arms. Due to lack of RCT evidence linking sorafenib to BSC in a prior sunitinib population this assumption is necessary to allow for BSC comparison to be made. Given the uncertainty around the impact of unobserved confounders, multiple approaches (STC and RENCOMP) were explored, with multiple scenario analyses	7.3.2.3

Assumption	Justification	Reference to section:
	included for both options.	
Data from non-RCT real world source (RENCOMP) can be compared to RCT data in an indirect comparison framework	Patients in clinical trials are expected to survive longer than patients in real-world clinical practice; this is reflected in the discrepancy in absolute survival times between the AXIS trial and the RENCOMP study. Despite the heterogeneity in patient characteristics and the different treatment settings (clinical trial versus real-world clinical practice), it is reasonable to assume that the proportional efficacy of adding 2nd-line sorafenib would be consistent between the two populations. Use of hazard ratio in indirect comparison allows for difference in magnitude in absolute survival times while retaining this proportional benefit (which is expected to be consistent between populations).	7.3.2.3
BSC and axitinib patients experience equivalent utility	In the absence of comparator utility values for treatment with BSC, a systematic review of advanced/mRCC health-related quality of life was carried out. This review did not identify any sources reporting utility measurements for patients in 2nd-line receiving best supportive care. In the absence of a relevant source from the literature, the assumption was made that BSC patients would experience the same utility as patients receiving active treatment with axitinib while in the PF and PD health states. .	7.4.3, 7.4.9

Abbreviations: AE, adverse event; BSC, best supportive care; mRCC, metastatic renal cell carcinoma; NICE, National Institute for Health and Clinical Excellence; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RPSFT; rank preserved structural failure time; SPC, summary of product characteristics; STC, simulated treatment comparison

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 *Please outline the aspects of the condition that most affect patients' quality of life.*

Clinical trials evaluating new treatment interventions for advanced/mRCC are increasingly incorporating HRQoL tools to assess disease and treatment related symptoms as symptom improvement is considered to an important measure in determining clinical benefit of treatment (57).

Two validated health status scales that are specific to RCC are increasingly being used to assess patients HRQoL in clinical trials: the Functional Assessment of Cancer Therapy (FACT)–Kidney Symptom Index (FKSI) and the RCC Symptom Index (133, 134).

Several important aspects of advanced/mRCC affect patients' quality of life particularly considering that the prognosis for patients with advanced/mRCC has historically been poor, with only 10% of patients surviving beyond 5 years.

Patients living with advanced/mRCC can suffer significant symptoms which can be related to tumour burden or metastatic site specific symptoms. In a US national cross sectional study (N=31 patients, N=10 caregivers) which systematically developed the content of an RCC patient symptom questionnaire using literature review, caregiver observation and above all, the perspective of patients with the disease, the top five symptoms reported by metastatic RCC patients (n=17) with metastatic disease were fatigue, weakness, worry, shortness of breath, and irritability (135).

In addition to the symptom burden, the psychosocial impact of diagnosis with an incurable, poor-prognosis malignancy such as advanced/mRCC is also considerable. Among patients participating in the study, patients identified psychosocial concerns including emotional distress, losing hope, worry about the illness progressing as important factors in affecting quality of life.

7.4.2 *Please describe how a patient's HRQL is likely to change over the course of the condition*

QoL is expected to remain relatively constant prior to progression and to diminish upon progression. QoL was maintained whilst patients remained on treatment (i.e. progression free), and declined when patients stopped study medication (mainly due to progression). Figure 15 in section 6.5.4 displays the change in EQ-5D by cycle for the AXIS study.

HRQL data derived from clinical trials

7.4.3 *If HRQL data were collected in the clinical trials identified in Section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.*

7.4.3.1 Base case – AXIS study

Utility data have been collected in the AXIS trial using EuroQoL-5D (EQ-5D) instrument, completed by the study patients at Day 1, every four weeks afterwards, at the end of study treatment or withdrawal and at follow up Day 28 (28 days after the last dose of active treatment). The quality of life analysis was based on the ITT population (the full analysis set). Data were available for the sum of scores from the EQ-5D questions that were also summarized with the mean and median at each assessment point. In contrast to the clinical efficacy information in the economic model, EQ-5D values are presented for the ITT population, as p-value analysis indicated no significant difference between any of the subgroups.

The baseline mean (SD) EQ-5D score (Day 1 of Cycle 1) for the axitinib arm was 0.732 (0.01).

To calculate the mean on-treatment utility for axitinib, an average on-treatment utility was calculated by averaging the EQ-5D index value at each time point in AXIS, weighted by the number of patients still on treatment at that time point, giving a mean (SD) on-treatment utility of 0.692 (0.275).

To model post-progression utilities, a weighted average utility estimate was calculated based on the mean utility at the end of treatment for all subjects, giving a mean (SD) utility of 0.610 (0.316).

In the absence of comparator utility values for treatment with BSC, a systematic review of advanced/mRCC health-related quality of life (reported in Section 7.4.5) was carried out. This review did not identify any sources reporting utility measurements for patients in second-line sunitinib-refractory advanced/mRCC receiving BSC. In the absence of a relevant source from the literature, the assumption was made that BSC patients would experience the same utility as patients receiving active treatment with axitinib. While patients with axitinib may expect to experience some reduction in health-related quality of life related to the treatment, they will also receive HRQoL benefit in terms of symptomatic control and disease stabilization. This assumption was tested and confirmed by the main clinical advisor for the economic model.

7.4.3.2 Scenario analysis – previous NICE utility estimates

In addition to the base case analysis described above, a scenario analysis was carried out with the utility figures used in several previous NICE appraisals to model second-line mRCC. As no previous Phase III RCTs have reported EQ-5D data in second-line advanced/mRCC, these utility figures (originally derived from a Phase II study of sunitinib in a cytokine-refractory patient population) have been used in every previous NICE appraisal in second-line advanced/mRCC. As these utility estimates are based on consensus between UK experts, the NICE appraisal committee and ERG groups from several appraisals, and allow for “like vs. like” comparability between axitinib and other previous advanced/mRCC appraisal.

The base-case and sensitivity analysis utility figures included in the model are described below in Section 7.4.9.

Mapping

7.4.4 ***If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide details.***

Mapping was not required for this appraisal.

HRQL studies

7.4.5 ***Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.***

Please refer to Section 10.12 (Appendix 12) for full details of the sustematic review.

7.4.6 ***Provide details of the studies in which HRQL is measured.***

Please refer to Section 10.12 (Appendix 12) for full details of the sustematic review.

7.4.7 ***Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.***

Please refer to Section 10.12 (Appendix 12) for full details of the sustematic review.

Adverse events

7.4.8 *Please describe how adverse events have an impact on HRQL.*

Because the HRQL estimates included in the AXIS trial reflect the adverse event profile associated with axitinib, the utility estimates included in the economic model are expected to reflect the adverse event profile of the treatment. Thus, no specific utility states were included to model adverse events.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 *Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in Sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.*

A summary of the QoL values used in the economic analysis is presented in Table 42.

Table 42: Summary of quality of life values for cost-effectiveness analysis

	State	Utility value, mean (SD)	Reference to section in submission
Base case	Progression Free	0.692 (0.275)	AXIS - weighted mean on-treatment utility for axitinib patients (7.4.3.1)
	Progressed	0.610 (0.316)	AXIS – mean utility at treatment discontinuation (7.4.3.1)
Scenario analysis	Progression Free	0.758 (0.03)	Previously utilised utility estimates from NICE 2nd-line advanced/mRCC appraisals (7.4.3.2)
	Progressed	0.683 (0.04)	

Abbreviations: mRCC, metastatic renal cell carcinoma; NICE, National Institute for Health and Clinical Excellence; SD, standard deviation.

7.4.10 *If clinical experts assessed the applicability of values available or estimated any values, please provide details.*

The details of this process have been described previously in Section 7.3.5.

7.4.11 *Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?*

HRQoL estimates used in the economic analysis reflect the patient experiences within each health state (PF and PD), HRQoL is assumed to be independent of treatment or BSC, adverse events or other factors. Estimates of the variance of utility values used for these health states were investigated through sensitivity analysis.

7.4.12 *Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?*

No health effects were excluded.

7.4.13 ***If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?***

Baseline quality of life was not directly assumed in the economic evaluation as patients were expecting to be in either the progression-free state or progressed disease state throughout the model.

7.4.14 ***Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.***

In the model HRQL values have been applied as a constant utility for each health state. However the method of calculation of the utility figures (described in 7.4.3.1) incorporates changes in patient utility by cycle as measured directly from the AXIS study.

7.4.15 ***Have the values in Sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.***

Values have not been amended.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 ***Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to Section 2.***

In line with recent NICE technology appraisals of advanced/mRCC technologies (29, 34, 76) the following range of cost inputs were considered in the modelling undertaken:

- Drug acquisition cost for axitinib. The standard daily dose is 10mg/day, with total cost per patient adjusted for dose intensity. No cost was assumed for axitinib drug administration as it is taken orally twice a day.
- NHS and PSS resource use associated with best supportive care and routine medical management.
- Treatment for AEs related to axitinib and/or BSC.

7.5.2 ***Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.***

Resource use was estimated based primarily on the PenTAG model, developed for the NICE bevacizumab, sorafenib, sunitinib and temsirolimus MTA (130), and supplemented with expert opinion and published sources. Wherever possible, the original NICE-validated costing source was utilised and updated with current NHS reference costs as outlined in section 7.5.6.

Resource identification, measurement and valuation studies

7.5.3 ***Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in Section 10.13, appendix 13. If the systematic search***

yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources.

A systematic review of resource use in RCC treatment was not conducted. Resource use was estimated based on clinical opinion and published sources. In addition, the everolimus STA manufacturer's submission and the PenTAG model, developed for the NICE bevacizumab, sorafenib, sunitinib and temsirolimus MTA were consulted for resource use (39, 130).

7.5.4 ***If clinical experts assessed the applicability of values available or estimated any values, please provide details.***

The details of this process have been described previously in Section 7.3.5.

Intervention and comparators' costs

7.5.5 ***Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to Sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.***

The cost of axitinib was modelled based on the recommended dosing schedule for the product (5mg BD). As axitinib is orally administered no administration costs were included. Treatment was assumed to continue to progression in keeping with the AXIS trial and recommended UK clinical practice for TKI treatment in advanced/mRCC.

Axitinib cost was adjusted for the relative dosing intensity observed in the AXIS trial (102%) and varied in probabilistic sensitivity analysis according to the observed standard deviation (35.2%). In addition, a scenario analysis was carried out to explore the impact of a lower dosing intensity. Expert opinion and observed clinical practice indicates that real-world dosing intensities are typically lower than those observed in clinical trials, so in keeping with clinician expert opinion and previous NICE appraisals in second-line advanced/mRCC (everolimus) an RDI of 80% was explored in scenario analysis.

Discontinuation may occur not only due to progression but also due to adverse events. This was incorporated to the model by applying a per-cycle cycle rate of adverse event related discontinuation.

This cycle rate was calculated from the data of the AXIS trial ITT population. Similar to the modelling of adverse event costs, it was assumed that adverse events are a function of treatment delivered and so would occur independently of patient characteristics, so an equivalent discontinuation due to AEs was assumed for the cytokine refractory and sunitinib refractory populations.

In the first 20 weeks of trial follow up 9.2 % of the patients discontinued axitinib due to AE. As more than 70-80 % of the patients progress before the 20th cycle, the discontinuation rate accounts for the average time at risk of discontinuation. This was done by calculating the mean PFS through 20 cycles, computed based on the Kaplan-Meier curve.

This cycle rate was used to calculate the number of patients still on treatment, by multiplying the number of patients before progression with the rate of continuation from the beginning, i.e. the cycle rate of continuation (one minus discontinuation rate) raised

to the number of cycles. This reflects that those patients who remain progression free only remain on treatment if they have not discontinued in any cycle up to the current cycle.

Based on the calculation, the probabilities of discontinuation per cycle applied to the model are 0.801% and 1.260% for the cytokine refractory and sunitinib refractory populations, respectively.

No drug costs were assumed for the comparator arm (best supportive care); all BSC costs are discussed in Sections 7.5.6 and 7.5.7.

Table 43: Unit costs associated with the technology in the economic model

Items	Intervention (confidence interval)	Justification
Technology cost	£3,517/cycle (28 days)	List price of Axitinib
Dosing intensity (base case)	102.0% (SD 35.2%)	Observed dosing intensity in AXIS study
Dosing intensity (scenario analysis)	80%	Intended to explore the impact of lower dosing intensity in real-world clinical practice; consistent with clinical opinion and previous NICE appraisals
Administration costs	n/a	Therapy administered orally with no associated costs for administration

Abbreviations: NICE, National Institute for Health and Clinical Excellence; PAS, patient access scheme; SD, standard deviation.

Health-state costs

7.5.6 ***Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in Section 7.2.4.***

The estimates of routine medical monitoring for the stable and progressed disease states were primarily based on those assumed in the PenTAG economic model (130) and the everolimus STA (39) . Assumptions made in these submissions were validated with expert clinical opinion to ensure consistency with current clinical practice. Costs were applied equally to the axitinib and BSC treatment arms as patients are expected to receive equivalent management regardless of treatment delivered. All costs were updated to current values, or inflated using the PSSRU Health Care Inflation Index for Hospital and Community Health Services where recent references were not available.

For the progression free health state, costs were included for patient monitoring (1 GP visit per cycle), tumour scans (1 scan per 3 cycles), and blood tests (1 test per cycle). For patient monitoring, the assumption was made that patients would receive ongoing management and drug dispensation by GP, in keeping with the assumptions made in the everolimus appraisal. However, a scenario analysis was carried out to examine the impact of assuming management by oncologist rather than GP.

For the progressed disease state, in keeping with the NICE MTA and everolimus submission, routine medical management costs for progressive disease were included

for one clinical consultation per month, 1.5 specialist palliative care community nurse visits per month, and pain medications.

In addition, a cost of death was included, using the reference from Coyle et al (1999) inflated to 2011 values (145)

Table 44: List of health states and associated costs in the economic model

Health states	Items	Mean frequency or duration	Unit cost (£)	Cost per cycle (£)
Progression free – Base case	GP visit[a]	1 visit per cycle	£53.00/visit	£53.00
	CT scan[b]	1 scan per 3 cycles	£160.00/scan	£53.33
	Blood test[c]	1 test per cycle	£3.36/test	£3.36
Total cost per cycle – Progression free state				**£109.69**
Progressed disease - Base Case	GP visit[d]	1 visit per cycle	£53.00/visit	£53.00
	Specialist community nurse[d]	3 visits / 8 weeks	£84.00	£126.00
	Pain medication[e]	28 vials per cycle	£5.00/dose	£140.00
Total cost per cycle – Progressed disease state				**£319.00**
Progression free – Scenario analysis assuming oncologist visits	Oncologist Visit[f]	1 visit per cycle	£120/visit	£120.00
	CT scan	-		As above
	Blood test			As above
Total cost per cycle – Progression free State (Scenario analysis)				**£176.69**
Progressed disease – Scenario analysis assuming oncologist visits	Oncologist Visit[f]	1 visit per cycle	£120/visit	£120.00
	Specialist community nurse[e]	-		As above
	Pain medication[e]			As above
Total cost per cycle – Progressed disease state (Scenario analysis)				**£386.00**

Sources: GP visits: Unit Costs of Health and Social Care 2011 (2011), Curtis L

[b]Code RA14Z Computerised Tomography Scan, more than three areas

[c]Code DAP823 Haematology [Excluding Anti-Coagulant Services]

Code 202AF- Band 2 Palliative/respite care: adult face-to-face NHS Trust and PCT combined Reference Costs 2007-08

[e]BNF section 4.7.2 Opioid analgesics (morphine sulphate 1 mg/mL, net price 50-mL vial = £5.00 http://www.medicinescomplete.com/mc/bnf/current/3502.htm#_3502)

[f]Medical Oncology Code 370 for the "National Schedule of Reference Costs Year : 2010-11 - NHS Trusts and PCTs combined Consultant Led: First Attendance Non-Admitted Face to Face"

*In all instances in this table "Cycle" refers to one 28-day model cycle

7.5.7 *Please summarise the costs for each adverse event listed in Section 6.9 (Adverse events). These should include the costs of therapies identified in Section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.*

The costs of adverse events for the axitinib and BSC arms were included in the PF health state, and added to the costs of ongoing resource use for this health state. It was assumed that AEs were resolved within one cycle. In alignment with previous NICE appraisals in advanced/mRCC, costs were applied only to grade 3/4 AEs with a occurring in at least 5% of the patient population.

For the axitinib arm, AEs were taken from the ITT population of the AXIS trial. The assumption was made of equivalent prevalence between the cytokine refractory and sunitinib refractory subgroups as AEs are expected to be related to treatment administered rather than patient characteristics. The AEs included for axitinib, which occurred in over 5% of the patient population and were judged by the clinical experts consulted to have an associated resource implication, were diarrhoea (with a prevalence of 10.0% in the full ITT safety population) and hypertension (with a prevalence of 15.3%).

For the BSC arm, AE profiles from the BSC treatment arms of the TARGET trial (Sorafenib versus BSC in a cytokine-refractory population) and RECORD-1 trial (Everolimus versus BSC in a TKI –refractory population) were pooled to determine an estimated AE profile for BSC. The only grade 3/4 adverse event with a prevalence of greater than 5% and an expected resource implication was anaemia, with a prevalence of 5.1% in the RECORD-1 trial.

Table 45 outlines the assumptions made and costs calculated for each of the AEs included in the model.

Table 45: List of adverse events and summary of costs included in the economic model

Adverse event	Study arm and frequency	Cost per episodes	Assumptions
Hypertension	Axitinib arm, 15.3%	£424.00	2 GP visits per year (cost per 11.7 minute visit = £36.00,) 2 district nurse visits per year (cost per visit = £38) Medication for hypertension (cost per year = £276 (inflated to 2011)
Source: [NICE clinical guideline 34]Hypertension medicine "Management of hypertension in adults in primary care: partial update: Costing Report" NICE (2006) (47) http://www.nice.org.uk/nicemedia/pdf/CG034costingreport.pdf Table 2: Future drug costs			
Diarrhoea	Axitinib arm, 10.0%	£544.00	2 days hospitalisation
Source: Code VC42Z Rehabilitation for other disorders			
Anaemia	BSC arm, 5.1%	£2,068.47	Reported in Mickisch et al 2010, inflated to 2011 costs (PSSRU tariff) (146)

Abbreviations: BSC, best supportive care; GP, general practitioner; PSSRU, Personal Sociak Services Research Unit.

Miscellaneous costs

7.5.8 *Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.*

All costs in the economic model have been described in the previous sections.

7.6 Sensitivity analysis

7.6.1 *Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.*

A number of structural assumptions have been examined in sensitivity analysis to explore the impacts on model outcomes. Specifically, assumptions were tested around the survival distribution chosen to extrapolate axitinib OS and PFS, the method of comparison to best supportive care, utility measurement, dosing intensity, and medical management. The specific scenario analyses tested are explored in Table 46.

Table 46: Scenario analyses

Parameter	Base case	Scenario analyses	Reference to section in submission
Method of extrapolation, cytokine refractory population			
Prior cytokine, PFS	Weibull	Lognormal, Gompertz	7.3.2
Prior cytokine, OS	Weibull	Loglogistic, Gompertz	7.3.2
Method of extrapolation, sunitinib refractory population			
Prior sunitinib, PFS	Weibull	Lognormal	7.3.2
Prior sunitinib, OS	Lognormal	Weibull	7.3.2
BSC comparison methodology			
Prior sunitinib, PFS	STC via ITT BSC population	STC via sunitinib-refractory population	7.3.2
Prior sunitinib, OS	STC via ITT BSC population	STC via sunitinib-refractory population Indirect comparison via RENCOMP	7.3.2
Utility estimate			
Axitinib and BSC utility estimates	AXIS study	2nd-line utilities (advanced/mRCC MTA and everolimus appraisal)	7.4.9
Dosing intensity			
Axitinib relative dosing intensity	AXIS study	Estimated real-world dosing intensity (Everolimus appraisal)	7.5.5
Medical management			
Ongoing medical management in pre-progression state	GP Management	Oncologist Management	7.5.6

Parameter	Base case	Scenario analyses	Reference to section in submission
Discount rate			
Discount Rate for costs and QALYs	3.5%	0%, 6%	7.2.6
Time Horizon			
Model time horizon	10 years	5 years, 15 years	7.2.6

Abbreviations: BSC, best supportive care; GP, general practitioner; ITT, intent-to-treat; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparison.

7.6.2 *Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in Section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.*

In addition to the scenario analyses discussed above, extensive univariate sensitivity analyses were conducted to test the sensitivity of the results to plausible variation of input parameters. Parameter values were varied ±20% to the base case value for the following parameters, with results displayed in a tornado diagram for all model base-cases:

- Utility estimates (progression-free and progressed disease)
- Discount rates
- Cost estimates:
  - Clinical consultation (Oncologist and GP)
  - CT scan
  - Blood count
  - Specialist nurse visit
  - District nurse visit
  - Number of GP visits and district nurse visit for the treatment of hypertension
  - Pain management medication
  - AE management
  - Relative dose intensity
  - Cost of death
  - Hazard ratios
- Survival analysis parameters (all individual parameters for Weibull, Gompertz, lognormal and loglogistic survival functions)
- OS and PFS hazard ratios from the cytokine refractory and sunitinib refractory (RENCOMP) indirect comparisons

7.6.3 *Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in Section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).*

Probabilistic sensitivity analyses (PSA) tested the impact of simultaneous random variation of model parameters using a second-order Monte Carlo simulation. In this analysis, each parameter (costs and outcomes) was assigned a probability distribution, and cost-effectiveness results associated with simultaneously selecting random values from those distributions were generated. The uncertainty in the survival probabilities has been represented through the joint variance-covariance matrix of these parameters together, including the treatment coefficients (147). Hazard ratios are the ratio of hazard in two groups, and the standard statistical approach to estimating variance and confidence intervals for such ratios is to assume normality on the log scale. Therefore uncertainty in hazard ratios for PFS and OS estimated from external sources (and not from patient level data) was represented using lognormal distributions according to the means and 95% confidence intervals. Since utilities are also constricted on the interval zero to one, they were varied according to beta-distributions based on the means and standard deviations reported in the AXIS trial. Costs were assumed to follow gamma distributions. Resource use counts follow discrete Poisson-distributions, whose conjugate distribution to describe the mean is the gamma distribution (148). The gamma distribution is also usually a good candidate to represent uncertainty in costs, because costs are constrained on the interval zero to positive infinity, and are often highly skewed. Since there was no information on the variability of some of these parameters, their 95% confidence interval was assumed to encompass ±25% of the mean value.

Acquisition cost of axitinib was not varied in PSA as it is considered certain. Relative dose intensity for axitinib, however, was allowed to follow a gamma distribution according to the mean and standard deviation of dose intensity reported in the AXIS study. The Monte Carlo simulation was run on a total of 1,000 iterations. Results of the probabilistic analysis were used to derive cost-effectiveness acceptability curves (CEACs). The STC adjustment factors are not included in the PSA. Theoretically when the underlying survival curves (i.e. axitinib survival) change, the whole calibration procedure would need to be redone. So the assumption in the model is that while the survival curve parameters for axitinib change as well as the hazard ratios (if applicable), the relationship between the survival curve parameters of axitinib and everolimus or BSC remains constant.

7.7 Results

Clinical outcomes from the model

7.7.1 *For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.*

Table 47 below presents a comparison of the median PFS and OS values for axitinib in the AXIS study by subgroup compared to the model base case estimates. As displayed below, all median estimates are within the 95% confidence intervals of the AXIS trial estimates. These results demonstrate that the modelled figures are comparable to the clinical trial results observed.

Table 47: Summary of model results for axitinib compared with clinical data

Outcome	Clinical trial result (months, median)	Model result (months, median)
Prior cytokine		
PFS	12.1 (10.1-13.9)	11.6
OS	29.4 (24.5-NE)	33.3
Prior sunitinib		
PFS	4.8 (4.5-6.4)	6.32
OS	15.2 (12.8-18.3)	16.6

Abbreviations: NE, not estimable; OS, overall survival; PFS, progression-free survival.

As BSC was modelled via an indirect comparison approach it was not possible to include a comparison of reported and predicted means, as this would equate to a naïve comparison.

7.7.2 *Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.*

Markov traces are available for all base case analyses considered (cytokine refractory and sunitinib refractory) in Appendix 19 . Additionally, Section 7.3.2 displays survival curves which demonstrate the output of the parametric survival equations used to model axitinib and BSC for all subgroups and sensitivity analyses considered.

7.7.3 *Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.*

Markov traces are available for all base case analyses considered (cytokine refractory and sunitinib refractory) in Appendix 19. Additionally, Section 7.3.2 displays survival curves which demonstrate the output of the parametric survival equations used to model axitinib and BSC for all subgroups and sensitivity analyses considered.

7.7.4 *Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.*

Predicted discounted health and cost outcomes by model state are presented in the following tables for each of the two subgroups (cytokine refractory and sunitinib refractory via STC).

Prior cytokine

Table 48: Model outputs by clinical outcomes – Axitinib cytokine refractory population

Outcome	LY	QALY	Cost (£)
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

Abbreviations: LY, life years; QALY, quality-adjusted life years.

Table 49: Model outputs by clinical outcomes – BSC cytokine refractory population

Outcome	LY	QALY	Cost (£)
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

Abbreviations: LY, life years; QALY, quality-adjusted life years.

Prior sunitinib

Table 50: Model outputs by clinical outcomes – Axitinib sunitinib refractory population

Outcome	LY	QALY	Cost (£)
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

Abbreviations: LY, life years; QALY, quality-adjusted life years.

Table 51: Model outputs by clinical outcomes – BSC sunitinib refractory population

Outcome	LY	QALY	Cost (£)
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

Abbreviations: LY, life years; QALY, quality-adjusted life years.

7.7.5 *Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.*

Table 52: Summary of QALY gain by health state

Health state	QALY (axitinib)	QALY (BSC)	Increment	Absolute increment	% absolute increment
Prior cytokine					
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior sunitinib					
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; PD, progressive disease; PFS, progression-free disease; QALY, quality-adjusted life year.

Table 53: Summary of costs by health state

Health state	Cost (axitinib)	Cost (BSC)	Increment	Absolute increment	% absolute increment
Prior cytokine					
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior sunitinib					
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; PD, progressive disease; PFS, progression-free disease.

Table 54: Summary of predicted resource use by category of cost

Item	Axitinib	BSC	Increment	Absolute increment	% absolute increment
Prior cytokine					
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Item	Axitinib	BSC	Increment	Absolute increment	% absolute increment
CT scans	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC in PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior sunitinib					
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT scans	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC in PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; PD, progressive disease; PFS, progression-free disease; STC, simulated treatment comparison.

Base-case analysis

7.7.6 ***Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.***

Base case results are presented in Table 55 using the list price for axitinib (without PAS).

Table 55: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Cytokine refractory							
BSC	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib refractory							
BSC	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; STC, simulated treatment comparison.

Sensitivity analyses

7.7.7 *Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.*

Sensitivity analyses are presented for the base case without the PAS.

Figure 36: Tornado diagram: Cytokine refractory population

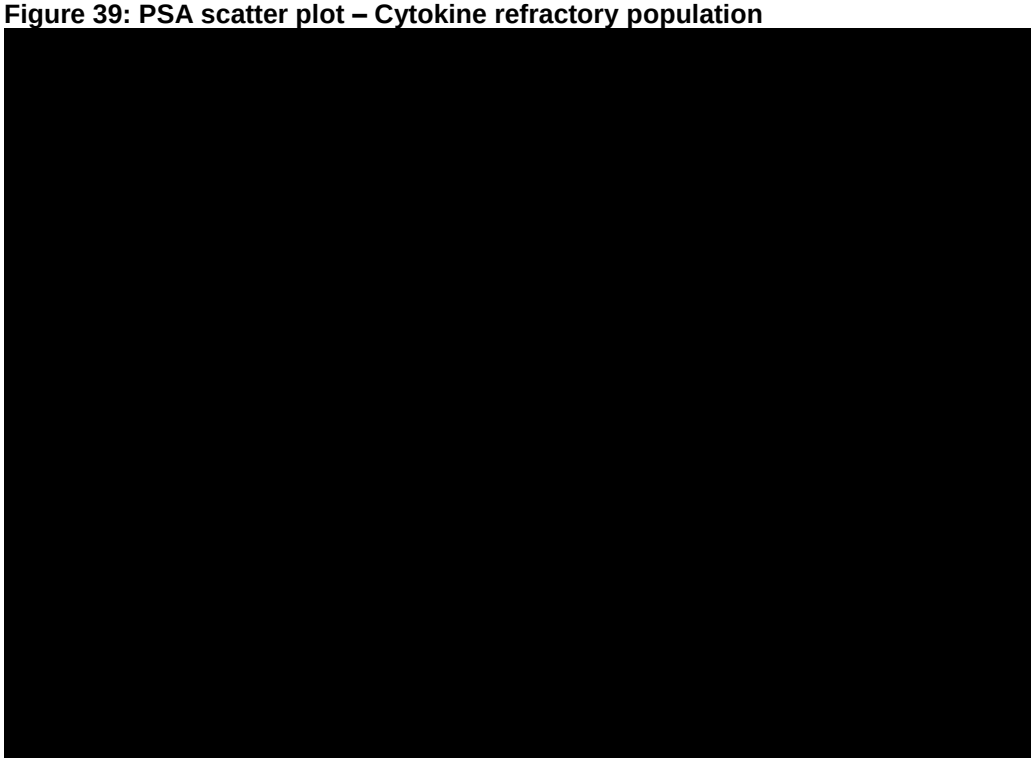
Figure 37: Tornado diagram – Sunitinib refractory population

7.7.8 *Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.*

Cytokine refractory population

Figure 38: Cost-effectiveness acceptability curve – Cytokine refractory population

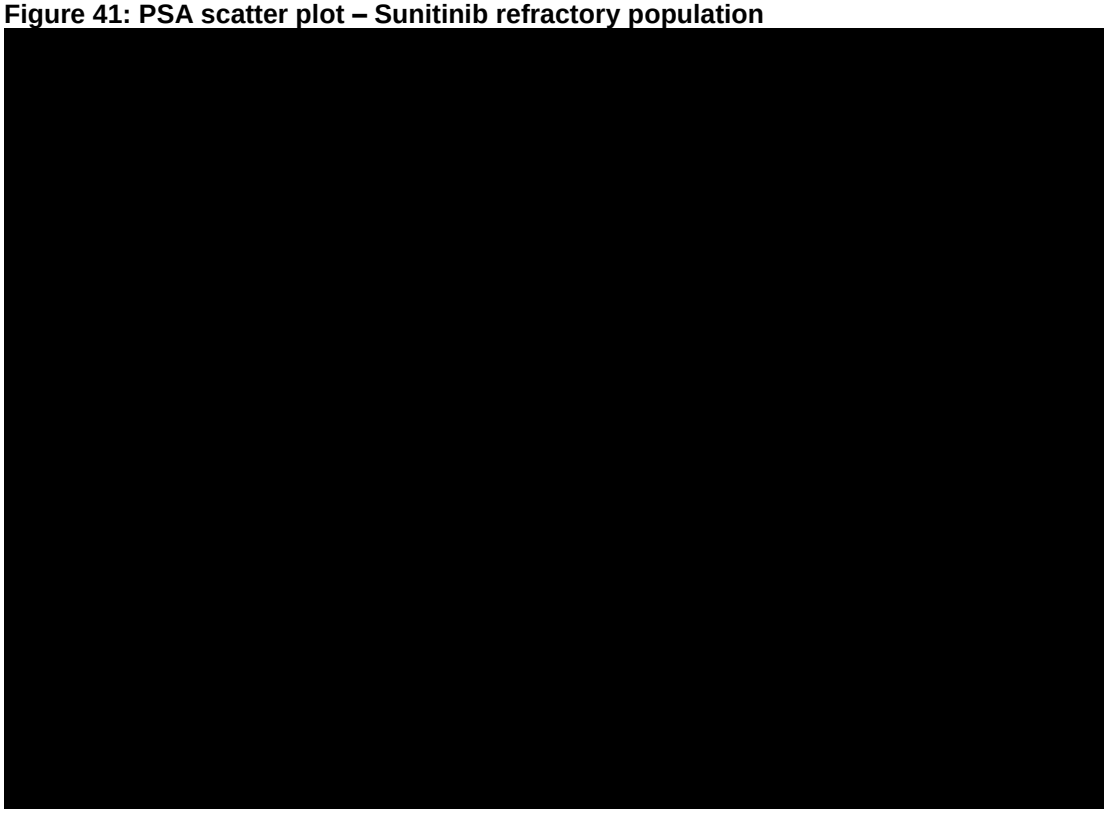
Figure 39: PSA scatter plot – Cytokine refractory population



Prior sunitinib population

Figure 40: Cost-effectiveness acceptability curve – Sunitinib refractory population

Figure 41: PSA scatter plot – Sunitinib refractory population



7.7.9 *Please present the results of scenario analysis. Include details of structural sensitivity analysis.*

Table 56: Scenario analysis results – Cytokine refractory population

Parameter	Base case	Scenario analysis	ICER
Base Case			[redacted]
Method of PFS extrapolation	Weibull	Lognormal Gompertz	[redacted] [redacted]
Method of OS extrapolation	Weibull	Loglogistic Gompertz	[redacted] [redacted]
Axitinib and BSC utility estimates	AXIS study	2nd-line utilities (advanced/mRCC MTA and everolimus appraisal)	[redacted]
Axitinib relative dosing intensity	AXIS study	Estimated real-world dosing intensity (Everolimus appraisal)	[redacted]
Ongoing medical management in pre-progression state	GP Management	Oncologist Management	[redacted]
Time horizon	10 years	5 years 15 years	[redacted] [redacted]
Discount Rate	3.5% costs and QALYs	0% 6%	[redacted] [redacted]

Abbreviationd: BSC, best supportive care; GP, general practitioner; ICER, incremental cost-effectiveness ratio; mRCC, metastatic renal cell carcinoma; MTA multiple technology appraisal; OS, overall survival; PFS, progression-free survival.

Table 57: Scenario analysis results – Sunitinib refractory population

Parameter	Base case	Scenario analysis		ICER
Base Case				[redacted]
Method of PFS comparison	STC Weibull via ITT RECORD-1 BSC population	STC lognormal via ITT RECORD-1 BSC		[redacted]
		STC Weibull via everolimus sunitinib refractory – BSC PFS		[redacted]
Method of OS comparison	STC lognormal via RECORD-1 ITT BSC population	STC Weibull via RECORD-1 ITT BSC		[redacted]
		STC Weibull via everolimus sunitinib refractory – BSC RPSFT		[redacted]
		RENCOMP	Weibull	[redacted]
			Lognormal	[redacted]
			Gompertz	[redacted]
Axitinib and BSC utility estimates	AXIS study	2nd-line utilities (advanced/mRCC MTA and everolimus appraisal)		[redacted]
Axitinib relative	AXIS study	Estimated real-world dosing		[redacted]

Parameter	Base case	Scenario analysis	ICER
dosing intensity		intensity (Everolimus appraisal)	
Medical management pre-progression	GP Management	Oncologist Management	[redacted]
Time horizon	10 years	5 years 15 years	[redacted] [redacted]
Discount Rate	3.5% costs and QALYs	0% 6%	[redacted] [redacted]

Abbreviationd: BSC, best supportive care; GP, general practitioner; ICER, incremental cost-effectiveness ratio; mRCC, metastatic renal cell carcinoma; MTA, multiple technology appraisal; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural time failure; STC, simulated treatment comparison.

7.7.10 *What were the main findings of each of the sensitivity analyses?*

7.7.11 *Key drivers of the cost-effectiveness results*

Sunitinib refractory subgroup

For the sunitinib refractory subgroup, the tornado diagram displaying the results +/-20% one-way sensitivity analysis is presented in Figure 37**.**

This analysis suggests that the cost-effectiveness of axitinib compared with BSC is stable to most changes in the model parameters with all variables resulting in upper bound ICERs [redacted]. The key sources of uncertainty in the model include the survival parameters for PFS and OS, progressed disease utilities, cost and relative dose intensity of axitinib.

Figure 40 and Figure 41 present a measure of the uncertainty around the base case estimates of cost- effectiveness (cost per QALY) from 1000 PSA replications, using cost-effectiveness acceptability curves (CEACs) and scatter plots. At a willingness to pay of £50,000/QALY, axitinib demonstrated [redacted] likelihood of being cost effective.

The scenario analyses indicate that the model is robust to the majority of structural assumptions made. [redacted].This indicates that the incremental survival benefit assumed over BSC is a key driver of the model result.

Prior cytokine subgroup

For the cytokine refractory subgroup, the tornado diagram displaying the results of the one-way sensitivity analysis varying all key model parameters ±20% from the base case values is presented in Figure 36. This analysis suggests that the cost-effectiveness of axitinib compared to BSC is stable to most changes in the model parameters, with the largest sources of uncertainty being utilities, survival parameters, and the OS hazard ratio of Axitinib vs. BSC via the TARGET study indirect comparison.

Figure 38 and Figure 39 present a graphical representation of the uncertainty around the base case estimates of cost- effectiveness (cost per QALY), using CEACs and scatter plots. The figure shows that where the NHS are willing to pay £50,000/QALY the probability that axitinib is cost-effective compared to BSC is approximately [redacted].

The scenario analyses examined for the cytokine refractory population indicate that the model base case can be viewed as a reasonably conservative estimate, with the majority of ICERs lower than the base case estimate. Key parameters which increased the ICER result included use of a lognormal model to extrapolate axitinib PFS, and a Gompertz model to extrapolate OS (which, as discussed in Section 7.3.2, are viewed as unrealistic estimates), use of oncologist management instead of GP management, and assuming no probability of discontinuation due to AEs.

7.8 Validation

7.8.1 *Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.*

Upon the completion of the model, a comprehensive and rigorous quality check was performed including validating the logical structure of the model, mathematical formulas and sequences of calculations, and the values of numbers supplied as model inputs. This validation process was performed by a peer-reviewer not involved in the model development. The process involves checking the intermediate calculations for references (whether they are linked to correct cells etc.) and implementation (whether correct signs for the parameters are used etc). The expected function of parameters is checked with extreme value sensitivity. The process also involves checking the functionality of any built-in Macro programs. This is a repeatable process that produces a checklist spreadsheet indicating the specific tasks performed, and their results returned (see accompanying spreadsheet). The original modeling team then responded to these comments by making changes to the model.

7.9 Subgroup analysis

7.9.1 *Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to Section 6.3.7.*

As the base case analysis includes the two subgroups based on prior therapy of the main AXIS study (cytokine refractory and sunitinib refractory), no further analysis was undertaken.

7.9.2 *Please clearly define the characteristics of patients in the subgroup.*

N/A

7.9.3 *Please describe how the statistical analysis was undertaken.*

N/A

7.9.4 *What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in Section 7.7.6 (Base-case analysis).*

N/A

7.9.5 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in Section 5.*

Whilst PFS and OS for the total population of patients included in the AXIS trial has been sub-analysed by performance status, this analysis has not been conducted for the sub-population of patients after failure of prior treatment with sunitinib or a cytokine because the resulting sub-groups are too small for interpretable results.

7.10 Interpretation of economic evidence

7.10.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

Sensitivity analysis indicates that the key driver of the model results is the QALY gain of axitinib over BSC. As the absolute survival estimates for axitinib from the AXIS trial can be viewed as relatively robust, the key source of uncertainty in the model is the absolute survival estimate produced by the model for treatment with BSC. The everolimus appraisal resulted in median BSC overall survival estimates of between 8.9 and 10.8 months, which were viewed as acceptable by the appraisal committee (149). However, clinical and patient opinion at the time indicated that this was likely viewed as an overestimate of the true BSC survival after failure of advanced/mRCC treatment with a TKI. This view is supported by the systematic review carried out to examine BSC survival post-sunitinib failure (see Section 6.7.10). Of the publications identified in this review, the maximum survival time demonstrated in a sunitinib refractory population was 11.6 months (median), in a subgroup of patients receiving sunitinib in clinical practice after progression (and likely still receiving benefit from the drug). The majority of the other estimates from the review in true sunitinib-refractory populations were in the 4-6 month range,substantially lower than the RECORD-1 estimate. Furthermore, this result was consistent with the 5.8 months median OS observed in the BSC arm of the RENCOMP study.

In comparison, the base case economic analysis explored in this model produces a BSC [redacted] (median 8.3 months), using the STC via the ITT BSC population and a lognormal extrapolation. Therefore, this can be viewed as a conservative analysis.

As with several previous NICE appraisals in advanced/mRCC, (sunitinib, pazopanib, everolimus) axitinib is expected to fulfil the end of life criteria.

Table 58 outlines the justification for applying the end of life criteria.

Table 58: End of life criteria for axitinib

Criteria	Justification
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	All model cases examined for sunitinib refractory patient population result in mean BSC survival estimates of less than 24 months. In addition, the systematic review of survival after sunitinib failure carried out to support this submission indicates that real-world survival times in absence of second-line treatment are expected to be less than a year.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment	Axitinib results in expected survival gains of greater than 3 months over BSC in all model cases evaluated.
The treatment is licensed or otherwise indicated, for small patient populations	The annual number of patients eligible to receive axitinib in the sunitinib or cytokine refractory patient population is 1580 in year 1, rising to 1743 in year 5.

7.10.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in Section 5?*

This economic evaluation directly reflects the two relevant sub-populations within the AXIS trial in line with axitinib marketing authorisation.

7.10.3 *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

Strengths of the economic evaluation

The model is reflective of both populations specified in the EMA license (sunitinib refractory and cytokine refractory). Despite the limited use of cytokines in the UK (in approximately 5% of advanced/mRCC patients) the model explores this subgroup alongside the more relevant sunitinib refractory population.

The model is aligned with previous NICE appraisals in terms of modelling methodology, resource utilisation estimates, utility figures, and other key inputs. Wherever possible, attempts have been made to align the model as closely with previous appraisals to allow for a “like with like” comparison. Moreover, the structure is directly based on the model from the NICE advanced/mRCC MTA as developed by PenTAG.

Another key strength of this analysis is its robustness to the multiple scenario analysis carried out to examine the impact of different parametric survival models on OS and PFS extrapolation. The method used to extrapolate was closely aligned with that used in previous appraisals and recommended by the NICE Decision Support Unit.

Another key strength of this analysis is its use of trial-based EQ-5D values to model axitinib. In contrast to previous appraisals, which used EQ-5D estimates from a Phase II single-arm study of sunitinib in cytokine refractory patients as a stand-in for second-line advanced/mRCC utility figures, this appraisal includes EQ-5D utilities measured directly in axitinib patients in the AXIS study. However, as the previous utility estimates have

been used by several NICE appraisal processes, these utility figures are also examined in scenario analysis.

Finally, while no direct evidence was available to compare axitinib with BSC, this analysis presents a robust examination of a number of different methodologies to estimate BSC PFS and OS for sunitinib refractory patients. Of the numerous methodologies evaluated, the approach chosen allows for a conservative estimate of axitinib incremental efficacy. The STC approach is able to overcome the two major shortcomings in the evidence network (confounding of the incremental OS measurement between axitinib and sorafenib in the AXIS study, and lack of unbiased evidence sources between sorafenib and BSC) to generate a conservative direct-to-BSC comparison. Thus, despite the limitations in the evidence network, the methodology employed to generate the BSC comparison can be viewed as producing a robust, conservative and clinically plausible estimate of BSC survival, as well as incremental axitinib benefit.

Weaknesses of the economic evaluation

The main weaknesses of this model are primarily around the uncertainty in estimating BSC overall survival. As previously discussed, the choice of sorafenib as the active comparator in the AXIS trial was intended to show head-to-head evidence against the perceived standard of care at the time of the trial design, resulting in a trial which was more relevant for decision-makers. As the UK has not adopted sorafenib (or any active treatment) for second-line advanced/mRCC, this active comparison design can in this case be viewed as the main limitation of the analysis.

As described in Section 6.10.2, there were a number of sources of confounding in the AXIS trial that resulted in a lack of apparent OS benefit with axitinib treatment compared with sorafenib. These included: the use of subsequent treatments after progression has occurred in the trial, which may have influenced OS (91); the fact that patients remained alive for on average 12 months after progression on study treatment, which may have diluted any OS benefit; and the use of an active comparator which may have reduced the likelihood of observing a benefit. However, previous studies have demonstrated the difficulty in demonstrating an OS benefit in advanced/mRCC even when placebo is used as the comparator (15, 34).

With respect to the cytokine refractory population, a key shortcoming of the model is the confounding of the axitinib-BSC OS indirect comparison due to crossover of the TARGET study. As statistical analysis correcting for cross-over was not in common practice when the TARGET study was reported, no such analysis has been carried out, and the current analysis censoring patients for crossover likely introduces a great deal of bias into the estimate.

For the prior-sunitinib simulated treatment comparison, there are several weaknesses to the analysis which should be mentioned. First, there are several inconsistencies between the patient populations in the AXIS and RECORD-1 trials, which creates an uncertain level of confounding between the two trials. Additionally, as the sunitinib-refractory BSC population from the RECORD-1 trial has never been fully reported, it was necessary to either make the assumption of equivalence between sunitinib refractory BSC patients and the ITT BSC population. However, the Motzer 2010 (97) publication indicates that sunitinib failure patients had much worse OS in RECORD-1 than non-prior sunitinib patients (HR=1.97, 1.42-2.75), and thus the assumption of equivalence between the ITT

RECORD-1 BSC population and the prior sunitinib population overestimates the OS for BSC and underestimates axitinib cost-effectiveness.

Another key limitation of the STC approach is the assumption of no unobserved covariates. In a traditional indirect comparison between RCTs, confounding due to unobserved covariates is assumed to be balanced out due to randomisation between trial arms. However, as the evidence network was not complete for the sunitinib refractory evidence network, this assumption was unavoidable. However, despite the aforementioned differences in patient populations between AXIS and RECORD-1, both are Phase III RCTs of advanced/mRCC in later-lines of therapy which likely shared similar trial centres investigators, and management practices. Additionally, both trials collected full sets of prognostic baseline characteristics. Finally, despite the necessity of the simplifying assumptions inherent in the STC method, the method results in a mean discounted BSC survival estimate of [redacted] which, although likely an overestimate based on current evidence and UK clinical practice, can be viewed as a conservative estimate.

The use of the RENCOMP study data in the sunitinib refractory analysis also contains several shortcomings. Again, the use of real-world data with patient matching via a Cox proportional hazard model relies on an assumption of no unobserved covariates. The RENCOMP study data includes an additional drawback over the STC in that the Swedish patient registries are not specific to oncology and thus did not report all the relevant advanced/mRCC prognostic factors. However, the choice of explanatory covariates in the RENCOMP analysis, which were intended to mirror as closely as possible the key prognostic factors in advanced/mRCC within the confines of the database, as well as the extensive sensitivity analysis carried out on the Cox model, diminishes the impact of potential confounding as much as possible. However, the assumption of no unobserved covariates is nonetheless an un-testable assumption underpinning this methodology

When the RENCOMP analysis is incorporated into the indirect comparison of axitinib to BSC and the cost effectiveness model, an additional shortcoming becomes apparent. While the RENCOMP analysis appears to provide an estimate of the real-world incremental OS benefit of sorafenib over BSC, the indirect analysis is still subject to the confounding in the OS estimate due to post progression treatment in the AXIS study. Thus, the analysis using the RENCOMP results still likely presents an unrealistic picture of BSC by substantially overestimating the overall survival. This is demonstrated by examining the survival estimates produced for BSC by the RENCOMP model analysis in comparison with the estimates identified in the literature.

Table 59 displays a breakdown of the analysis of the predicted discounted survival estimates from the RENCOMP model cases, alongside the base-case and scenario-analysis STC estimates. As this table illustrates, use of the RENCOMP hazard ratio result in substantially higher BSC survival estimates than either the model base case or the estimated figure from the everolimus RCT. Thus, the indirect anlysis using the RENCOMP results together with the HR from the AXIS trial appears to substantially overestimate survival times for BSC, and as a result underestimates the cost-effectiveness of axitinib versus BSC.

Table 59: Survival predictions and model results, base case and scenario analyses

	Axitinib arm survival estimate	BSC arm survival estimate	Survival benefit, months	Survival benefit, %	ICER
Axitinib: Base case					
STC lognormal via RECORD-1 ITT BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib: OS Scenario Analyses					
STC Weibull via RECORD-1 ITT BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RENCOMP, lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RENCOMP, Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive car; ICER, incremental cost-effectiveness ratio; STC, simulated treatment comparison;

In conclusion, this economic analysis is reflective of both populations specified in the EMA license, is aligned with previous NICE appraisals in structure and design, and displays robust and thorough sensitivity analysis resulting in a realistic long-term survival estimate for axitinib and a likely overly high, and thus conservative survival estimate for BSC. Despite the uncertainty and assumptions necessary to model the BSC comparison, the analysis demonstrates that axitinib in the sunitinib refractory population has been robustly and conservatively demonstrated to be close to the accepted criteria for a cost-effective end of life treatment and could be considered good value for money for adoption by the NHS. In the cytokine refractory population ICER with the current evidence is higher than than willingness to pay thresholds used for other 'end of life' treatments which have been recently approved by NICE, although the true ICER is likely lower than the one reported in this analysis.

7.10.4 *What further analyses could be undertaken to enhance the robustness/completeness of the results?*

Several potential analyses could increase the certainty and validity of these results; primarily by strengthening the comparison with best supportive care. More specifically:

1. STC versus sunitinib-refractory, RPSFT-adjusted BSC population from RECORD-1

As discussed in the STC section, one key shortcoming of this STC analysis was the assumption of similar characteristics and outcomes between the RECORD-1 ITT BSC population and the prior sunitinib BSC population. The RECORD-1 prior sunitinib-only patient population has never been published as a fully specified subgroup. An analysis which displayed the patient characteristics, median (RPSFT adjusted) OS and PFS

figures for this subgroup would allow for a more accurate STC to be carried out. However, as the Motzer (2010) study reported (97), sunitinib failure patients displayed substantially much worse OS in RECORD-1 than non-prior sunitinib patients (HR=1.97, 1.42-2.75). This then indicates that the assumption of equivalence between the RECORD-1 ITT BSC population and the prior sunitinib population may be viewed as a conservative estimate and as a result underestimates the cost-effectiveness of axitinib versus BSC.

2. RPSFT analysis of TARGET study

A key shortcoming of the cytokine-refractory sub-population analysis is the confounding due to crossover of the TARGET study. As statistical analysis correcting for cross-over were not in common practice when the TARGET study was reported, no such analysis has been carried out, and the current analysis censoring patients for crossover likely introduces selection bias of sorafenib over BSC. Adjusting OS data of the TARGET study using statistical analysis to correct for cross-over would allow for a more accurate axitinib vs. BSC indirect comparison in the cytokine refractory subgroup.

3. Placebo-controlled trial of axitinib vs. BSC in the sunitinib and cytokine refractory populations

Given the difficulty inherent in this analysis of developing a comparison between axitinib and BSC, comparative evidence of axitinib versus placebo in a second-line (sunitinib or cytokine-refractory population) would substantially decrease the uncertainty in this analysis. However, given the current license having been granted on the basis of the comparative AXIS study, ethical considerations of conducting placebo-controlled studies in diseases where multiple standards of care exist in the comparative setting, and the time and resource constraints inherent in developing such a trial, it is not feasible to collect this data at this time.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The number of incident patients calculated for year 1 is displayed in Table 60.

Table 60: Year 1 annual incident patients eligible for treatment with axitinib

Description	Percentage	Patient Flow
Number of newly diagnosed kidney cancers in the UK	100%	N=8163
Percentage of kidney cancers which are RCC	90%	N=7347
Percentage of patients expected to be diagnosed with stage III and IV disease, or to recur with stage III/IV disease after previous stage I/II diagnosis	27% stage III 14% stage IV, 33.3% recurrent	Stage III/IV: N=3012 Stage I&II recurrent: N=1443
Percentage of total eligible for first-line treatment (Overall proportion of patients that present with an ECOG performance status of 0 or 1 AND are suitable for immunotherapy) (68.0%)	68.00%	N=3030
Percentage of first-line patients eligible for treatment expected to receive Sunitinib and Cytokines	77% Sunitinib, 5% Cytokines	Sunitinib N=2333 Cytokines N=151
Percentage of first-line patients going on to receive treatment with a second-line agent	63.6%	Prior Sunitinib **N=1484** Prior Cytokines **N=96**

To calculate the increase in incident patients for the subsequent 5 years from approval, the percentage change in annual incidence from RCC in the UK between 1993 (11.1/100,000) and 2009 (15.5/100,000) (13) (the time span for which incidence data is available) was calculated and annualized, assuming a linear growth rate, giving a projected annual increase in incidence of 2.48%. This rate was applied to the incident population from year 1 to calculate projected incident population for the subsequent 5 years following approval, as displayed in Table 61.

Table 61: Projected increase in eligible patient incidence, years 1-5

	Year 1	Year 2	Year 3	Year 4	Year 5
Prior sunitinib	1484	1521	1558	1597	1636
Prior cytokine	96	99	101	104	106
Total	1580	1619	1659	1700	1743

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

As displayed in Table 60, it is assumed that 63.6% of eligible first line patients will receive second line treatment, based on Pfizer internal marketing projections. Additionally, the estimate of advanced/mRCC patients who are receiving first-line treatment with sunitinib and cytokines, respectively was assumed to be constant for the 5-year period assessed in this calculation.

8.3 What assumption(s) were made about market share (when relevant)?

[redacted]

Table 62: Axitinib anticipated market share, year 1–5

	Year 1	Year 2	Year 3	Year 4	Year 5
Axitinib market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior sunitinib patients receiving axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cytokine patients receiving axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

No additional incremental costs other than drug costs, routine medical management, and adverse event management are projected to be required to bring axitinib into clinical practice.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

All cost estimates included in this section are based on the inputs and outcomes of the axitinib economic model described in section 7. This calculation determines the total number of patients treated each year, and then assigns the patients to second-line treatments based on market share inputs. The total cost per treatment is determined by multiplying the annual cost of each treatment, as determined in the cost-effectiveness analysis, by the number of patients assigned to each regimen. The total budget impact over 5 years assuming axitinib introduction is then compared to the corresponding figure

if axitinib is not adopted and BSC is provided to the full population. Both figures are then compared to calculate the expected incremental budget impact of axitinib introduction.

8.6 Were there any estimates of resource savings? If so, what were they?

No relevant cost offsets or resource savings have been identified. As axitinib will be provided alongside the current standard of care (BSC) rather than replacing an active treatment comparator, no cost offsets relating to drug, medical management or AE management have been identified.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The following projected cost estimates per patient were used from the economic model to determine year 1-5 costs by subgroup and comparator.

Table 63: Cost per patient as predicted by the economic model, years 1-5

	Year 1	Year 2	Year 3	Year 4	Year 5
Axitinib, sunitinib refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib, cytokine refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC, sunitinib refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC, cytokine refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The following tables display the expected 5-year cost of treatment with axitinib introduction, the expected 5-year cost of treatment without axitinib introduction, and the expected annual budget impact, respectively. These values are total cost figures, incorporating cost of drug (without PAS), routine medical management, and management of AEs.

Table 64: Total annual treatment costs - with axitinib introduction

Eligible patients	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Sunitinib refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving axitinib					
Sunitinib refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving BSC					
Sunitinib refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Eligible patients	Year 1	Year 2	Year 3	Year 4	Year 5
Cytokine refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total annual treatment costs - with axitinib introduction					
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care.

Table 65: Total annual treatment costs - without axitinib introduction

Eligible patients	Year 1	Year 2	Year 3	Year 4	Year 5
Sunitinib refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving BSC					
Sunitinib refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total annual treatment costs - without axitinib introduction					
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care.

Table 66: Incremental budget impact of axitinib introduction

	Year 1	Year 2	Year 3	Year 4	Year 5
Overall budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No additional opportunities for savings have been identified.

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10 Appendices

10.1 Appendix 1

10.1.1 *SPC/IFU, scientific discussion or drafts.*

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg of axitinib.

Excipients with known effect:

Each film-coated tablet contains 33.6 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Red oval film-coated tablet debossed with “Pfizer” on one side and “1 XNB” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

4.2 Posology and method of administration

Treatment with Inlyta should be conducted by a physician experienced in the use of anticancer therapies.

Posology

The recommended starting dose of axitinib is 5 mg twice daily.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs that cannot be managed by concomitant medicinal products or dose adjustments.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose adjustments

Dose increase or reduction is recommended based on individual safety and tolerability.

Patients who tolerate the axitinib starting dose of 5 mg twice daily with no adverse reactions > Grade 2 (i.e. without severe adverse reactions according to the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) for two consecutive weeks may have their dose increased to 7 mg twice daily unless the patient's blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment. Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7 mg twice daily may have their dose increased to a maximum of 10 mg twice daily.

Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). When dose reduction is necessary, the axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily.

Dose adjustment is not required on the basis of patient age, race, gender, or body weight.

Concomitant strong CYP3A4/5 inhibitors

Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 inhibition potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended. Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy (see section 4.4). If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered (see section 4.5).

Concomitant strong CYP3A4/5 inducers

Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 induction potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co-administered, a gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). If co-administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer (see section 4.5).

Special populations

Elderly patients (≥ 65 years): No dose adjustment is required (see sections 4.4 and 5.2).

Renal impairment: No dose adjustment is required (see section 5.2). Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 ml/min.

Hepatic impairment: No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of axitinib in children (< 18 years) have not been established. No data are available.

Method of administration

Axitinib should be taken orally twice daily approximately 12 hours apart with or without food (see section 5.2). Axitinib tablets should be swallowed whole with a glass of water.

4.3 Contraindications

Hypersensitivity to axitinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Specific safety events should be monitored before initiation of, and periodically throughout, treatment with axitinib as described below.

Hypertension

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypertension was very commonly reported (see section 4.8). The median onset time for hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension, despite use of anti-hypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension (see section 4.2).

In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (see below), a diagnostic brain magnetic resonance image (MRI) should be considered.

Thyroid dysfunction

In a controlled clinical study with axitinib for the treatment of patients with RCC, events of hypothyroidism and, to a lesser extent, hyperthyroidism, were reported (see section 4.8).

Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial embolic and thrombotic events

In clinical studies with axitinib, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic or thrombotic event within the previous 12 months.

Venous embolic and thrombotic events

In clinical studies with axitinib, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous embolic or thrombotic event within the previous 6 months.

Elevation of haemoglobin or haematocrit

Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib (see section 4.8, polycythaemia). An increase in red blood cell mass may increase the risk of embolic and thrombotic events.

Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.

Haemorrhage

In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Gastrointestinal perforation and fistula formation

In clinical studies with axitinib, events of gastrointestinal perforation and fistulas were reported (see section 4.8).

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.

Wound healing complications

No formal studies of the effect of axitinib on wound healing have been conducted.

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Posterior reversible encephalopathy syndrome

In clinical studies with axitinib, events of posterior reversible encephalopathy syndrome (PRES) were reported (see section 4.8).

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with signs or symptoms of PRES, temporarily interrupt or

permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.

Proteinuria

In clinical studies with axitinib, proteinuria, including that of Grade 3 severity, was reported (see section 4.8).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment (see section 4.2).

Liver-related adverse events

In a controlled clinical study with axitinib for the treatment of patients with RCC, liver-related events were reported. The most commonly reported liver-related adverse reactions included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin (see section 4.8). No concurrent elevations of ALT (> 3 times the upper limit of normal [ULN]) and bilirubin (> 2 times the ULN) were observed.

In a clinical dose-finding study, concurrent elevations of ALT (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose).

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with axitinib.

Hepatic impairment

In clinical studies with axitinib, the systemic exposure to axitinib was approximately two-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (see section 4.2).

Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

Elderly patients (≥ 65 years) and race

In a controlled clinical study with axitinib for the treatment of patients with RCC, 34% of patients treated with axitinib were ≥ 65 years of age. The majority of patients were White (77%) or Asian (21%). Although greater sensitivity to develop adverse reactions in some older patients and Asian patients cannot be ruled out, overall, no major differences were observed in the safety and effectiveness of axitinib between patients who were ≥ 65 years of age and non-elderly, and between White patients and patients of other races.

No dosage adjustment is required on the basis of patient age or race (see sections 4.2 and 5.2).

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that axitinib is metabolised primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 inhibitors

Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2 -fold and C_{max} 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 and CYP2C19 inhibitors

CYP1A2 and CYP2C19 constitute minor (< 10%) pathways in axitinib metabolism. The effect of strong inhibitors of these isozymes on axitinib pharmacokinetics has not been

studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes.

CYP3A4/5 inducers

Rifampicin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and C_{max} by 71% of a single 5 mg dose of axitinib in healthy volunteers.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [St. John's wort]) may decrease axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 induction by smoking

CYP1A2 constitutes a minor (< 10%) pathway in axitinib metabolism. The effect of smoking-related CYP1A2 induction on axitinib pharmacokinetics has not been fully characterised. The risk of decreased axitinib plasma concentrations should be considered when administering axitinib to smokers.

In vitro studies of CYP and UGT inhibition and induction

In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co-administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).

In vitro studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co-administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.

In vitro studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore co-administration of axitinib is not expected to reduce the plasma concentration of co-administered CYP1A1, CYP1A2, or CYP3A4/5 substrates *in vivo*.

In vitro studies with P-glycoprotein

In vitro studies indicated that axitinib inhibits P-glycoprotein. However, axitinib is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, *in vivo*.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data regarding the use of axitinib in pregnant women. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product.

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Breast-feeding

It is unknown whether axitinib is excreted in human milk. A risk to the suckling child cannot be excluded. Axitinib should not be used during breast-feeding.

Fertility

Based on non-clinical findings, axitinib has the potential to impair reproductive function and fertility in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with axitinib.

4.8 Undesirable effects

Summary of the safety profile

The most important serious adverse reactions reported in patients receiving axitinib were arterial embolic and thrombotic events, venous embolic and thrombotic events, haemorrhage (including gastrointestinal haemorrhage, cerebral haemorrhage and haemoptysis), gastrointestinal perforation and fistula formation, hypertensive crisis, and posterior reversible encephalopathy syndrome. These risks, including appropriate action to be taken, are discussed in section 4.4.

The most common (≥ 20%) adverse reactions observed following treatment with axitinib were diarrhoea, hypertension, fatigue, dysphonia, nausea, decreased appetite, and palmar-plantar erythrodysaesthesia (hand-foot) syndrome.

Tabulated list of adverse reactions

Table 1 presents adverse reactions reported in patients who received axitinib in a pivotal clinical study for the treatment of patients with RCC (see section 5.1).

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data). The current safety database for axitinib is too small to detect rare and very rare adverse reactions (< 1/1,000).

Categories have been assigned based on absolute frequencies in the clinical study data. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in the RCC study in patients who received axitinib (N= 359)

System Organ Class	Frequency Category	Adverse Reactions	All Grades[a] %	Grade 3[a] %	Grade 4[a] %
Blood and	Common	Anaemia	2.8	0.3	0

System Organ Class	Frequency Category	Adverse Reactions	All Grades[a] %	Grade 3[a] %	Grade 4[a] %
lymphatic system disorders		Thrombocytopenia	1.7	0.3	0
	Uncommon	Neutropenia	0.3	0.3	0
		Polycythaemia[b]	0.3	0	0
		Leukopenia	0.3	0	0
Endocrine disorders	Very Common	Hypothyroidism[b]	18.4	0.3	0
	Uncommon	Hyperthyroidism[b]	0.6	0	0
Metabolism and nutrition disorders	Very Common	Decreased appetite	28.4	3.3	0.3
	Common	Dehydration	4.7	2.5	0
	Uncommon	Hyperkalaemia	0.8	0.6	0
		Hypercalcaemia	0.6	0	0
Nervous system disorders	Very Common	Headache	10.3	0.6	0
		Dysgeusia	10.3	0	0
	Common	Dizziness	5.6	0	0
	Uncommon	Posterior reversible encephalopathy syndrome	0.3	0.3	0
Ear and labyrinth disorders	Common	Tinnitus	2.2	0	0
Vascular disorders	Very Common	Hypertension	39.3	15.3	0.3
		Haemorrhage[b, c]	10.6	0.3	0.3
	Common	Venous embolic and thrombotic events[b, c]	1.9	0.8	0.8
		Arterial embolic and thrombotic events[b, c]	1.1	1.1	0
	Uncommon	Hypertensive crisis	0.6	0.3	0.3

System Organ Class	Frequency Category	Adverse Reactions	All Grades[a] %	Grade 3[a] %	Grade 4[a] %
Respiratory, thoracic and mediastinal disorders	Very Common	Dysphonia	28.1	0	0
	Common	Dyspnoea	7.0	0.3	0
		Cough	5.3	0	0
		Oropharyngeal pain	3.3	0	0
Gastrointestinal disorders	Very Common	Diarrhoea	51.3	9.7	0.3
		Vomiting	16.7	1.4	0
		Nausea	28.7	1.4	0
		Stomatitis	14.5	1.4	0
		Constipation	12.3	0	0
	Common	Abdominal pain	8.4	0.6	0.3
		Upper abdominal pain	6.1	0.3	0
		Dyspepsia	7.8	0	0
		Flatulence	4.5	0	0
		Haemorrhoids	2.2	0	0
	Uncommon	Gastrointestinal perforation[b, d]	0.3	0	0.3
		Anal fistula[b]	0.3	0	0
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia (hand-foot syndrome)	27.3	5.0	0
		Rash	11.7	0.3	0
		Dry skin	10.0	0	0
	Common	Pruritus	5.8	0	0
		Erythema	2.2	0	0

System Organ Class	Frequency Category	Adverse Reactions	All Grades[a] %	Grade 3[a] %	Grade 4[a] %
		Alopecia	3.3	0	0
Musculoskeletal and connective tissue disorders	Common	Myalgia	5.3	0.6	0.3
		Arthralgia	8.6	0.6	0
		Pain in extremity	8.9	0.3	0
Renal and urinary disorders	Very Common	Proteinuria	10.3	3.1	0
	Common	Renal failure[e]	1.1	0.6	0
General disorders and administration site conditions	Very Common	Fatigue	34.8	9.5	0.3
		Asthaenia[c]	17.5	3.6	0.3
		Mucosal inflammation	15.0	1.4	0
Investigations	Very Common	Weight decreased	16.4	1.4	0
	Common	Thyroid stimulating hormone increased	4.5	0	0
		Lipase increased	2.2	0.6	0
		Alanine aminotransferase increased	1.9	0.3	0
		Aspartate aminotransferase increased	1.1	0.3	0
		Alkaline phosphatase increased	1.4	0	0
		Amylase increased	1.7	0	0
	Uncommon	Blood bilirubin increased	0.6	0	0
		Creatinine increased	0.6	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

[b] See Description of selected adverse reactions section

[c] Fatal (Grade 5) cases were reported

[d] Adverse reaction is all-causality incidence

[e] Including acute renal failure

Description of selected adverse reactions

Thyroid dysfunction (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 18.4% of patients and hyperthyroidism was reported in 0.6% of patients. Thyroid stimulating hormone (TSH) increased was reported as an adverse reaction in 4.5% of patients receiving axitinib. During routine laboratory assessments, in patients who had TSH < 5 µU/ml before treatment, elevations of TSH to ≥ 10 µU/ml occurred in 32.2% of patients receiving axitinib.

Venous embolic and thrombotic events (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, venous embolic and thrombotic adverse reactions were reported in 1.9% of patients receiving axitinib. Grade 3/4 venous embolic and thrombotic adverse reactions were reported in 1.7% of patients receiving axitinib (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis). Fatal pulmonary embolism was reported in one patient (0.3%) receiving axitinib.

Arterial embolic and thrombotic events (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, Grade 3/4 arterial embolic and thrombotic adverse reactions were reported in 1.1% of patients receiving axitinib. The most frequent arterial embolic and thrombotic event was transient ischemic attack (0.8%). A fatal cerebrovascular accident was reported in one patient (0.3%) receiving axitinib. In monotherapy studies with axitinib (N=699), arterial embolic and thrombotic adverse reactions (including transient ischemic attack, myocardial infarction, and cerebrovascular accident) were reported in 1.0% of patients receiving axitinib.

*Polycythaemia (*see *Elevation of haemoglobin or haematocrit* in section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, polycythaemia was reported as an adverse reaction in 0.3% of patients receiving axitinib. Routine laboratory assessments detected elevated haemoglobin above ULN in 9.7% of patients receiving axitinib. In four clinical studies with axitinib for the treatment of patients

with RCC (N=537), elevated haemoglobin above ULN was observed in 13.6% receiving axitinib.

Haemorrhage (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC that excluded patients with untreated brain metastasis, haemorrhagic adverse reactions were reported in 10.6% of patients receiving axitinib. The most common haemorrhagic adverse reactions in patients treated with axitinib were epistaxis (5.3%), haematuria (1.4%), rectal haemorrhage (1.1%) and gingival bleeding (1.1%). Grade $\geq$ 3 haemorrhagic adverse reactions were reported in 0.8% of patients receiving axitinib (including cerebral haemorrhage, gastric haemorrhage and lower gastrointestinal haemorrhage). Fatal haemorrhage was reported in one patient (0.3%) receiving axitinib (gastric haemorrhage). In monotherapy studies with axitinib (N=699), haemoptysis was reported as an adverse reaction in 1.6% of patients, including one case (0.1%) of a Grade $\geq$ 3 event.

Gastrointestinal perforation and fistula formation (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation was reported in one patient (0.3%, all-causality incidence) receiving axitinib. In monotherapy studies with axitinib (N=699), fistulas were reported in 0.7% of patients (all-causality incidence) and fatal gastrointestinal perforation was reported in one patient (0.1%).

4.9 Overdose

There is no specific treatment for axitinib overdose.

In a controlled clinical study with axitinib for the treatment of patients with RCC, one patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal haemoptysis.

In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE17

Mechanism of action

Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target *in vivo* and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.

Effect on QTc interval

In a randomised, 2-way crossover study, 35 healthy subjects were administered a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole for 7 days. Results of this study indicated that axitinib plasma exposures up to two-fold greater than therapeutic levels expected following a 5 mg dose, did not produce clinically-significant QT interval prolongation.

Clinical efficacy

The safety and efficacy of axitinib were evaluated in a randomised, open-label, multicenter Phase 3 study. Patients (N=723) with advanced RCC whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomised (1:1) to receive axitinib (n=361) or sorafenib (n=362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (53.8%) had received one prior sunitinib-based therapy, 251 patients (34.7%) had received one prior cytokine-based therapy (interleukin-2 or interferon-alpha), 59 patients (8.2%) had received one prior bevacizumab-based therapy, and 24 patients (3.3%) had received one prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups with regard to age, gender, race,

Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

In the overall patient population and the two main subgroups (prior sunitinib treatment and prior cytokine treatment), there was a statistically significant advantage for axitinib over sorafenib for the primary endpoint of PFS (see Table 2 and Figures 1, 2 and 3). The magnitude of median PFS effect was different in the subgroups by prior therapy. Two of the subgroups were too small to give reliable results (prior temsirolimus treatment or prior bevacizumab treatment). There were no statistically significant differences between the arms in OS in the overall population or in the subgroups by prior therapy.

Table 2. Efficacy results

Endpoint / Study Population	Axitinib	Sorafenib	HR (95% CI)	p-value
Overall ITT	**N = 361**	**N = 362**		
Median PFS [a,b] in months (95% CI)	6.8 (6.4, 8.3)	4.7 (4.6, 6.3)	0.67 (0.56, 0.81)	< 0.0001[c]
Median OS [d] in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
ORR [b,e] % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[f] (1.41, 3.00)	0.0001[g]
Prior sunitinib treatment	**N = 194**	**N = 195**		
Median PFS [a,b] in months (95% CI)	4.8 (4.5, 6.5)	3.4 (2.8, 4.7)	0.74 (0.58, 0.94)	0.0063[h]
Median OS [d] in months (95% CI)	15.2 (12.8, 18.3)	16.5 (13.7, 19.2)	1.00 (0.78, 1.27)	NS
ORR [b,e] % (95% CI)	11.3 (7.2, 16.7)	7.7 (4.4, 12.4)	1.48[f] (0.79, 2.75)	NS
Prior cytokine treatment	**N = 126**	**N = 125**		
Median PFS [a,b] in months (95% CI)	12.0 (10.1, 13.9)	6.6 (6.4, 8.3)	0.52 (0.38, 0.72)	< 0.0001[h]
Median OS [d] in months (95% CI)	29.4 (24.5, NE)	27.8 (23.1, 34.5)	0.81 (0.56, 1.19)	NS
ORR [b,e] % (95% CI)	32.5 (24.5, 41.5)	13.6 (8.1, 20.9)	2.39[f] (1.43-3.99)	0.0002[i]

CI=Confidence interval, HR=Hazard ratio (axitinib/sorafenib); ITT: Intent-to-treat; NE: not estimable; NS: not statistically significant; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

[a] Time from randomization to progression or death due to any cause, whichever occurs first. Cutoff date: 03 June 2011.

[b] Assessed by independent radiology review according to RECIST.

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy.

[d] Cutoff date: 01 November 2011.

[e] Cutoff date: 31 August 2010.

[f] Risk ratio is used for ORR. A risk ratio > 1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio < 1 indicated a higher likelihood of responding in the sorafenib arm.

[g] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior therapy.

[h] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[i] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status.

Figure 1. Kaplan-Meier curve of progression-free survival by independent assessment for the overall population

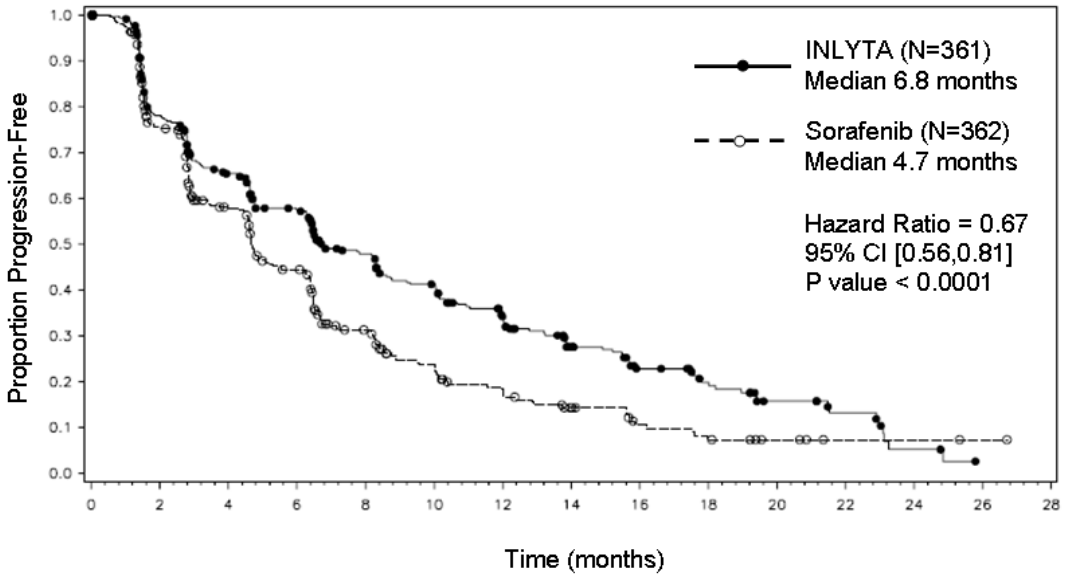


Figure 2. Kaplan-Meier curve of progression-free survival by independent assessment for the prior sunitinib subgroup

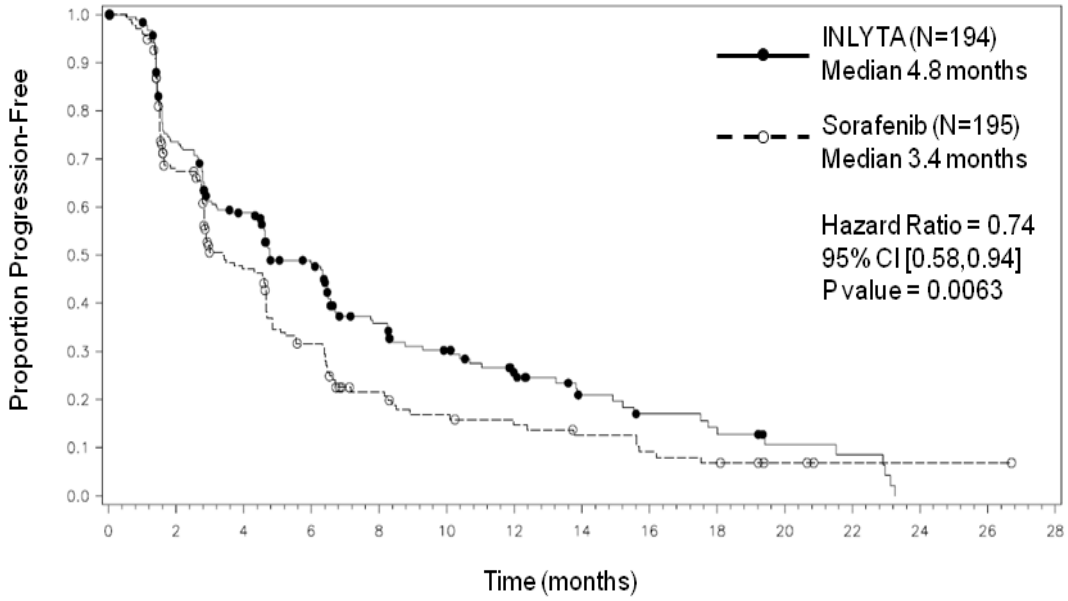
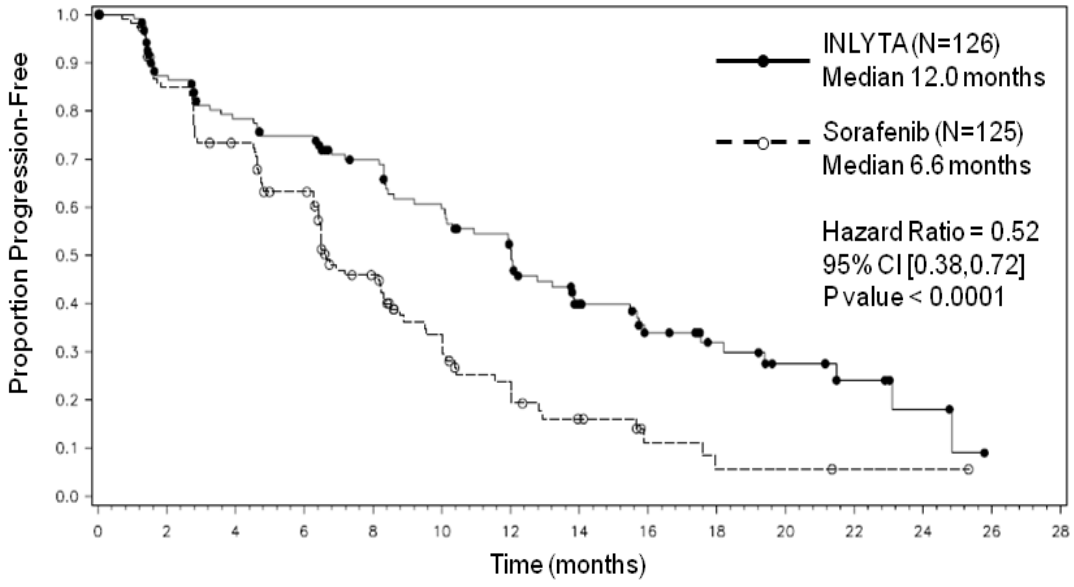


Figure 3. Kaplan-Meier curve of progression-free survival by independent assessment for the prior cytokine subgroup



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with axitinib in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

After oral administration of axitinib tablets, the mean absolute bioavailability is 58% compared to intravenous administration. The plasma half life of axitinib ranges from 2.5 to 6.1 hours. Dosing of axitinib at 5 mg twice daily resulted in less than two-fold accumulation compared to administration of a single dose. Based on the short half-life of axitinib, steady state is expected within 2 to 3 days of the initial dose.

Absorption and distribution

Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of axitinib with median T_{max} ranging from 2.5 to 4.1 hours. Administration of axitinib with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting. Axitinib may be administered with or without food (see section 4.2).

The average C_{max} and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg. *In vitro* binding of axitinib to human plasma proteins is > 99% with preferential binding to albumin and moderate binding to α_1-acid glycoprotein. At the 5 mg twice daily dose in the fed state, the geometric mean peak plasma concentration and 24-hour AUC were 27.8 ng/ml and 265 ng.h/ml, respectively, in patients with advanced RCC. The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Biotransformation and elimination

Axitinib is metabolised primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

Following oral administration of a 5 mg radioactive dose of axitinib, 30-60% of the radioactivity was recovered in faeces and 23% of the radioactivity was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in faeces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special populations

Elderly patients, gender, and race

Population pharmacokinetic analyses in patients with advanced cancer (including advanced RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

Paediatric population

Axitinib has not been studied in patients < 18 years of age.

Hepatic impairment

In vitro and *in vivo* data indicate that axitinib is primarily metabolised by the liver.

Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately two-fold) in subjects with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see section 4.2 for dose adjustment recommendations).

Renal impairment

Unchanged axitinib is not detected in the urine.

Axitinib has not been studied in subjects with renal impairment. In clinical studies with axitinib for the treatment of patients with RCC, patients with serum creatinine > 1.5 times the ULN or calculated creatinine clearance < 60 ml/min were excluded. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required.

5.3 Preclinical safety data

Repeat dose toxicity

Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were the gastrointestinal, haematopoietic, reproductive, skeletal and dental systems, with No Observed Adverse Effect Levels (NOAEL) approximately equivalent to or below expected human exposure at the recommended clinical starting dose (based on AUC levels).

Carcinogenicity

Carcinogenicity studies have not been performed with axitinib.

Genotoxicity

Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays *in vitro*. A significant increase in polyploidy was observed *in vitro* at concentrations > 0.22 µg/ml, and an elevation in micronucleated polychromatic erythrocytes was observed *in vivo* with No Observed Effect Level (NOEL) 69-fold the expected human exposure. Genotoxicity findings are not considered clinically relevant at exposure levels observed in humans.

Reproduction toxicity

Axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. These findings were observed in mice at exposure levels approximately 12-fold the expected human exposure, and in dogs at exposure levels below the expected human exposure. There was no effect on mating or fertility in male mice at exposure levels approximately 57-fold the expected human exposure. Findings in females included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice at all doses tested, with exposure levels at the lowest dose approximately 10-fold the expected human exposure.

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, at exposure levels below the expected human exposure. Perinatal and postnatal developmental toxicity studies have not been conducted.

Toxicity findings in immature animals

Reversible physeal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately six-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for more than 1 month at exposure levels similar to the expected human exposure. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Magnesium stearate

Film-coating:

Hypromellose

Titanium dioxide (E171)

Lactose monohydrate

Triacetin (E1518)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister. Each pack contains 28 or 56 tablets.

HDPE bottle with a silica gel desiccant and a polypropylene closure containing 180 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich, Kent CT13 9NJ

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Inlyta 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of axitinib.

Excipients with known effect:

Each film-coated tablet contains 58.8 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Red triangular film-coated tablet debossed with “Pfizer” on one side and “5 XNB” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

4.2 Posology and method of administration

Treatment with Inlyta should be conducted by a physician experienced in the use of anticancer therapies.

Posology

The recommended starting dose of axitinib is 5 mg twice daily.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs that cannot be managed by concomitant medicinal products or dose adjustments.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose adjustments

Dose increase or reduction is recommended based on individual safety and tolerability.

Patients who tolerate the axitinib starting dose of 5 mg twice daily with no adverse reactions > Grade 2 (i.e. without severe adverse reactions according to the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) for two consecutive weeks may have their dose increased to 7 mg twice daily unless the patient's blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment. Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7 mg twice daily may have their dose increased to a maximum of 10 mg twice daily.

Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). When dose reduction is necessary, the axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily.

Dose adjustment is not required on the basis of patient age, race, gender, or body weight.

Concomitant strong CYP3A4/5 inhibitors

Co-administration of axitinib with strong CYP3A4/5 inhibitors may increase axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 inhibition potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib to approximately half the dose (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily) is recommended. Management of some adverse reactions may require temporary or permanent discontinuation of axitinib therapy (see section 4.4). If co-administration of the strong inhibitor is discontinued, a return to the axitinib dose used prior to initiation of the strong CYP3A4/5 inhibitor should be considered (see section 4.5).

Concomitant strong CYP3A4/5 inducers

Co-administration of axitinib with strong CYP3A4/5 inducers may decrease axitinib plasma concentrations (see section 4.5). Selection of an alternate concomitant medicinal product with no or minimal CYP3A4/5 induction potential is recommended.

Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inducers, if a strong CYP3A4/5 inducer must be co-administered, a gradual dose increase of axitinib is recommended. Maximal induction with high-dose strong CYP3A4/5 inducers has been reported to occur within one week of treatment with the inducer. If the dose of axitinib is increased, the patient should be monitored carefully for toxicity. Management of some adverse reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib therapy (see section 4.4). If co-administration of the strong inducer is discontinued, the axitinib dose should be immediately returned to the dose used prior to initiation of the strong CYP3A4/5 inducer (see section 4.5).

Special populations

Elderly patients (≥ 65 years): No dose adjustment is required (see sections 4.4 and 5.2).

Renal impairment: No dose adjustment is required (see section 5.2). Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 ml/min.

Hepatic impairment: No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of axitinib in children (< 18 years) have not been established. No data are available.

Method of administration

Axitinib should be taken orally twice daily approximately 12 hours apart with or without food (see section 5.2). Axitinib tablets should be swallowed whole with a glass of water.

4.3 Contraindications

Hypersensitivity to axitinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Specific safety events should be monitored before initiation of, and periodically throughout, treatment with axitinib as described below.

Hypertension

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypertension was very commonly reported (see section 4.8). The median onset time for hypertension (systolic blood pressure > 150 mmHg or diastolic blood pressure

> 100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension, despite use of anti-hypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension (see section 4.2).

In case of severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (see below), a diagnostic brain magnetic resonance image (MRI) should be considered.

Thyroid dysfunction

In a controlled clinical study with axitinib for the treatment of patients with RCC, events of hypothyroidism and, to a lesser extent, hyperthyroidism, were reported (see section 4.8).

Thyroid function should be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism or hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial embolic and thrombotic events

In clinical studies with axitinib, arterial embolic and thrombotic events (including transient ischemic attack, myocardial infarction, cerebrovascular accident and retinal artery occlusion) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial embolic or thrombotic event within the previous 12 months.

Venous embolic and thrombotic events

In clinical studies with axitinib, venous embolic and thrombotic events (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis) were reported (see section 4.8).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous embolic or thrombotic event within the previous 6 months.

Elevation of haemoglobin or haematocrit

Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib (see section 4.8, polycythaemia). An increase in red blood cell mass may increase the risk of embolic and thrombotic events.

Haemoglobin or haematocrit should be monitored before initiation of, and periodically throughout, treatment with axitinib. If haemoglobin or haematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease haemoglobin or haematocrit to an acceptable level.

Haemorrhage

In clinical studies with axitinib, haemorrhagic events were reported (see section 4.8).

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding, and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Gastrointestinal perforation and fistula formation

In clinical studies with axitinib, events of gastrointestinal perforation and fistulas were reported (see section 4.8).

Symptoms of gastrointestinal perforation or fistula should be periodically monitored for throughout treatment with axitinib.

Wound healing complications

No formal studies of the effect of axitinib on wound healing have been conducted.

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Posterior reversible encephalopathy syndrome

In clinical studies with axitinib, events of posterior reversible encephalopathy syndrome (PRES) were reported (see section 4.8).

PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with signs or symptoms of PRES, temporarily interrupt or permanently discontinue axitinib treatment. The safety of reinitiating axitinib therapy in patients previously experiencing PRES is not known.

Proteinuria

In clinical studies with axitinib, proteinuria, including that of Grade 3 severity, was reported (see section 4.8).

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment (see section 4.2).

Liver-related adverse events

In a controlled clinical study with axitinib for the treatment of patients with RCC, liver-related events were reported. The most commonly reported liver-related adverse reactions included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin (see section 4.8). No concurrent elevations of ALT (> 3 times the upper limit of normal [ULN]) and bilirubin (> 2 times the ULN) were observed.

In a clinical dose-finding study, concurrent elevations of ALT (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose).

Liver function tests should be monitored before initiation of, and periodically throughout, treatment with axitinib.

Hepatic impairment

In clinical studies with axitinib, the systemic exposure to axitinib was approximately two-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B) (see section 4.2).

Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

Elderly patients (≥ 65 years) and race

In a controlled clinical study with axitinib for the treatment of patients with RCC, 34% of patients treated with axitinib were ≥ 65 years of age. The majority of patients were White (77%) or Asian (21%). Although greater sensitivity to develop adverse reactions in some older patients and Asian patients cannot be ruled out, overall, no major differences were observed in the safety and effectiveness of axitinib between patients who were ≥ 65 years of age and non-elderly, and between White patients and patients of other races.

No dosage adjustment is required on the basis of patient age or race (see sections 4.2 and 5.2).

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that axitinib is metabolised primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 inhibitors

Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2-fold and C_{max} 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and

telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 and CYP2C19 inhibitors

CYP1A2 and CYP2C19 constitute minor (< 10%) pathways in axitinib metabolism. The effect of strong inhibitors of these isozymes on axitinib pharmacokinetics has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes.

CYP3A4/5 inducers

Rifampicin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and C_{max} by 71% of a single 5 mg dose of axitinib in healthy volunteers.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and *Hypericum perforatum* [St. John's wort]) may decrease axitinib plasma concentrations. Selection of concomitant medicinal products with no or minimal CYP3A4/5 induction potential is recommended. If a strong CYP3A4/5 inducer must be co-administered, a dose adjustment of axitinib is recommended (see section 4.2).

CYP1A2 induction by smoking

CYP1A2 constitutes a minor (< 10%) pathway in axitinib metabolism. The effect of smoking-related CYP1A2 induction on axitinib pharmacokinetics has not been fully characterised. The risk of decreased axitinib plasma concentrations should be considered when administering axitinib to smokers.

In vitro studies of CYP and UGT inhibition and induction

In vitro studies indicated that axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations.

In vitro studies indicated that axitinib has a potential to inhibit CYP1A2. Therefore, co-administration of axitinib with CYP1A2 substrates may result in increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).

In vitro studies also indicated that axitinib has the potential to inhibit CYP2C8. However, co-administration of axitinib with paclitaxel, a known CYP2C8 substrate, did not result in

increased plasma concentrations of paclitaxel in patients with advanced cancer, indicating lack of clinical CYP2C8 inhibition.

In vitro studies in human hepatocytes also indicated that axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5. Therefore co-administration of axitinib is not expected to reduce the plasma concentration of co-administered CYP1A1, CYP1A2, or CYP3A4/5 substrates *in vivo*.

In vitro studies with P-glycoprotein

In vitro studies indicated that axitinib inhibits P-glycoprotein. However, axitinib is not expected to inhibit P-glycoprotein at therapeutic plasma concentrations. Therefore, co-administration of axitinib is not expected to increase the plasma concentration of digoxin, or other P-glycoprotein substrates, *in vivo*.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data regarding the use of axitinib in pregnant women. Based on the pharmacological properties of axitinib, it may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). Axitinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with this medicinal product.

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Breast-feeding

It is unknown whether axitinib is excreted in human milk. A risk to the suckling child cannot be excluded. Axitinib should not be used during breast-feeding.

Fertility

Based on non-clinical findings, axitinib has the potential to impair reproductive function and fertility in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised that they may experience events such as dizziness and/or fatigue during treatment with axitinib.

4.8 Undesirable effects

Summary of the safety profile

The most important serious adverse reactions reported in patients receiving axitinib were arterial embolic and thrombotic events, venous embolic and thrombotic events, haemorrhage (including gastrointestinal haemorrhage, cerebral haemorrhage and haemoptysis), gastrointestinal perforation and fistula formation, hypertensive crisis, and posterior reversible encephalopathy syndrome. These risks, including appropriate action to be taken, are discussed in section 4.4.

The most common (≥ 20%) adverse reactions observed following treatment with axitinib were diarrhoea, hypertension, fatigue, dysphonia, nausea, decreased appetite, and palmar-plantar erythrodysaesthesia (hand-foot) syndrome.

Tabulated list of adverse reactions

Table 1 presents adverse reactions reported in patients who received axitinib in a pivotal clinical study for the treatment of patients with RCC (see section 5.1).

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data). The current safety database for axitinib is too small to detect rare and very rare adverse reactions (< 1/1,000).

Categories have been assigned based on absolute frequencies in the clinical study data. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in the RCC study in patients who received axitinib (N= 359)

System Organ Class	Frequency Category	Adverse Reactions	All Grades[a] %	Grade 3[a] %	Grade 4[a] %
Blood and lymphatic system disorders	Common	Anaemia	2.8	0.3	0
		Thrombocytopenia	1.7	0.3	0
	Uncommon	Neutropenia	0.3	0.3	0
		Polycythaemia[b]	0.3	0	0
		Leukopenia	0.3	0	0
Endocrine disorders	Very Common	Hypothyroidism[b]	18.4	0.3	0
	Uncommon	Hyperthyroidism[b]	0.6	0	0
Metabolism and nutrition disorders	Very Common	Decreased appetite	28.4	3.3	0.3
	Common	Dehydration	4.7	2.5	0
	Uncommon	Hyperkalaemia	0.8	0.6	0
		Hypercalcaemia	0.6	0	0
Nervous system disorders	Very Common	Headache	10.3	0.6	0
		Dysgeusia	10.3	0	0
	Common	Dizziness	5.6	0	0
	Uncommon	Posterior reversible encephalopathy syndrome	0.3	0.3	0
Ear and labyrinth disorders	Common	Tinnitus	2.2	0	0
Vascular disorders	Very Common	Hypertension	39.3	15.3	0.3
		Haemorrhage[b, c]	10.6	0.3	0.3
	Common	Venous embolic and thrombotic events[b, c]	1.9	0.8	0.8

System Organ Class	Frequency Category	Adverse Reactions	All Grades[a] %	Grade 3[a] %	Grade 4[a] %
		Arterial embolic and thrombotic events[b, c]	1.1	1.1	0
	Uncommon	Hypertensive crisis	0.6	0.3	0.3
Respiratory, thoracic and mediastinal disorders	Very Common	Dysphonia	28.1	0	0
	Common	Dyspnoea	7.0	0.3	0
		Cough	5.3	0	0
		Oropharyngeal pain	3.3	0	0
Gastrointestinal disorders	Very Common	Diarrhoea	51.3	9.7	0.3
		Vomiting	16.7	1.4	0
		Nausea	28.7	1.4	0
		Stomatitis	14.5	1.4	0
		Constipation	12.3	0	0
	Common	Abdominal pain	8.4	0.6	0.3
		Upper abdominal pain	6.1	0.3	0
		Dyspepsia	7.8	0	0
		Flatulence	4.5	0	0
		Haemorrhoids	2.2	0	0
	Uncommon	Gastrointestinal perforation[b, d]	0.3	0	0.3
		Anal fistula[b]	0.3	0	0
Skin and subcutaneous tissue disorders	Very Common	Palmar-plantar erythrodysaesthesia (hand-foot syndrome)	27.3	5.0	0
		Rash	11.7	0.3	0

System Organ Class	Frequency Category	Adverse Reactions	All Grades[a] %	Grade 3[a] %	Grade 4[a] %
		Dry skin	10.0	0	0
	Common	Pruritus	5.8	0	0
		Erythema	2.2	0	0
		Alopecia	3.3	0	0
Musculoskeletal and connective tissue disorders	Common	Myalgia	5.3	0.6	0.3
		Arthralgia	8.6	0.6	0
		Pain in extremity	8.9	0.3	0
Renal and urinary disorders	Very Common	Proteinuria	10.3	3.1	0
	Common	Renal failure[e]	1.1	0.6	0
General disorders and administration site conditions	Very Common	Fatigue	34.8	9.5	0.3
		Asthaenia[c]	17.5	3.6	0.3
		Mucosal inflammation	15.0	1.4	0
Investigations	Very Common	Weight decreased	16.4	1.4	0
	Common	Thyroid stimulating hormone increased	4.5	0	0
		Lipase increased	2.2	0.6	0
		Alanine aminotransferase increased	1.9	0.3	0
		Aspartate aminotransferase increased	1.1	0.3	0
		Alkaline phosphatase increased	1.4	0	0
		Amylase increased	1.7	0	0

System Organ Class	Frequency Category	Adverse Reactions	All Grades[a] %	Grade 3[a] %	Grade 4[a] %
	Uncommon	Blood bilirubin increased	0.6	0	0
		Creatinine increased	0.6	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

[b] See Description of selected adverse reactions section

[c] Fatal (Grade 5) cases were reported

[d] Adverse reaction is all-causality incidence

[e] Including acute renal failure

Description of selected adverse reactions

Thyroid dysfunction (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 18.4% of patients and hyperthyroidism was reported in 0.6% of patients. Thyroid stimulating hormone (TSH) increased was reported as an adverse reaction in 4.5% of patients receiving axitinib. During routine laboratory assessments, in patients who had TSH < 5 µU/ml before treatment, elevations of TSH to ≥ 10 µU/ml occurred in 32.2% of patients receiving axitinib.

Venous embolic and thrombotic events (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, venous embolic and thrombotic adverse reactions were reported in 1.9% of patients receiving axitinib. Grade 3/4 venous embolic and thrombotic adverse reactions were reported in 1.7% of patients receiving axitinib (including pulmonary embolism, deep vein thrombosis, and retinal vein occlusion/thrombosis). Fatal pulmonary embolism was reported in one patient (0.3%) receiving axitinib.

Arterial embolic and thrombotic events (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, Grade 3/4 arterial embolic and thrombotic adverse reactions were reported in 1.1% of patients receiving axitinib. The most frequent arterial embolic and thrombotic event was transient ischemic attack (0.8%). A fatal cerebrovascular accident was reported in one

patient (0.3%) receiving axitinib. In monotherapy studies with axitinib (N=699), arterial embolic and thrombotic adverse reactions (including transient ischemic attack, myocardial infarction, and cerebrovascular accident) were reported in 1.0% of patients receiving axitinib.

*Polycythaemia (*see *Elevation of haemoglobin or haematocrit* in section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, polycythaemia was reported as an adverse reaction in 0.3% of patients receiving axitinib. Routine laboratory assessments detected elevated haemoglobin above ULN in 9.7% of patients receiving axitinib. In four clinical studies with axitinib for the treatment of patients with RCC (N=537), elevated haemoglobin above ULN was observed in 13.6% receiving axitinib.

Haemorrhage (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC that excluded patients with untreated brain metastasis, haemorrhagic adverse reactions were reported in 10.6% of patients receiving axitinib. The most common haemorrhagic adverse reactions in patients treated with axitinib were epistaxis (5.3%), haematuria (1.4%), rectal haemorrhage (1.1%) and gingival bleeding (1.1%). Grade $\geq$ 3 haemorrhagic adverse reactions were reported in 0.8% of patients receiving axitinib (including cerebral haemorrhage, gastric haemorrhage and lower gastrointestinal haemorrhage). Fatal haemorrhage was reported in one patient (0.3%) receiving axitinib (gastric haemorrhage). In monotherapy studies with axitinib (N=699), haemoptysis was reported as an adverse reaction in 1.6% of patients, including one case (0.1%) of a Grade $\geq$ 3 event.

Gastrointestinal perforation and fistula formation (see section 4.4)

In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation was reported in one patient (0.3%, all-causality incidence) receiving axitinib. In monotherapy studies with axitinib (N=699), fistulas were reported in 0.7% of patients (all-causality incidence) and fatal gastrointestinal perforation was reported in one patient (0.1%).

4.9 Overdose

There is no specific treatment for axitinib overdose.

In a controlled clinical study with axitinib for the treatment of patients with RCC, one patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal haemoptysis.

In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE17

Mechanism of action

Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target *in vivo* and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.

Effect on QTc interval

In a randomised, 2-way crossover study, 35 healthy subjects were administered a single oral dose of axitinib (5 mg) in the absence and presence of 400 mg ketoconazole for 7 days. Results of this study indicated that axitinib plasma exposures up to two-fold greater than therapeutic levels expected following a 5 mg dose, did not produce clinically-significant QT interval prolongation.

Clinical efficacy

The safety and efficacy of axitinib were evaluated in a randomised, open-label, multicenter Phase 3 study. Patients (N=723) with advanced RCC whose disease had progressed on or after treatment with one prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomised (1:1) to

receive axitinib (n=361) or sorafenib (n=362). The primary endpoint, progression-free survival (PFS), was assessed using a blinded independent central review. Secondary endpoints included objective response rate (ORR) and overall survival (OS).

Of the patients enrolled in this study, 389 patients (53.8%) had received one prior sunitinib-based therapy, 251 patients (34.7%) had received one prior cytokine-based therapy (interleukin-2 or interferon-alpha), 59 patients (8.2%) had received one prior bevacizumab-based therapy, and 24 patients (3.3%) had received one prior temsirolimus-based therapy. The baseline demographic and disease characteristics were similar between the axitinib and sorafenib groups with regard to age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, geographic region, and prior treatment.

In the overall patient population and the two main subgroups (prior sunitinib treatment and prior cytokine treatment), there was a statistically significant advantage for axitinib over sorafenib for the primary endpoint of PFS (see Table 2 and Figures 1, 2 and 3). The magnitude of median PFS effect was different in the subgroups by prior therapy. Two of the subgroups were too small to give reliable results (prior temsirolimus treatment or prior bevacizumab treatment). There were no statistically significant differences between the arms in OS in the overall population or in the subgroups by prior therapy.

Table 2. Efficacy results

Endpoint / Study Population	Axitinib	Sorafenib	HR (95% CI)	p-value
Overall ITT	**N = 361**	**N = 362**		
Median PFS [a,b] in months (95% CI)	6.8 (6.4, 8.3)	4.7 (4.6, 6.3)	0.67 (0.56, 0.81)	< 0.0001[c]
Median OS [d] in months (95% CI)	20.1 (16.7, 23.4)	19.2 (17.5, 22.3)	0.97 (0.80, 1.17)	NS
ORR [b,e] % (95% CI)	19.4 (15.4, 23.9)	9.4 (6.6, 12.9)	2.06[f] (1.41, 3.00)	0.0001[g]
Prior sunitinib treatment	**N = 194**	**N = 195**		
Median PFS [a,b] in months (95% CI)	4.8 (4.5, 6.5)	3.4 (2.8, 4.7)	0.74 (0.58, 0.94)	0.0063[h]
Median OS [d] in months (95% CI)	15.2 (12.8, 18.3)	16.5 (13.7, 19.2)	1.00 (0.78, 1.27)	NS
ORR [b,e] % (95% CI)	11.3 (7.2, 16.7)	7.7 (4.4, 12.4)	1.48[f] (0.79, 2.75)	NS

Prior cytokine treatment	N = 126	N = 125		
Median PFS [a,b] in months (95% CI)	12.0 (10.1, 13.9)	6.6 (6.4, 8.3)	0.52 (0.38, 0.72)	< 0.0001[h]
Median OS [d] in months (95% CI)	29.4 (24.5, NE)	27.8 (23.1, 34.5)	0.81 (0.56, 1.19)	NS
ORR [b,e] % (95% CI)	32.5 (24.5, 41.5)	13.6 (8.1, 20.9)	2.39[f] (1.43-3.99)	0.0002[i]

CI=Confidence interval, HR=Hazard ratio (axitinib/sorafenib); ITT: Intent-to-treat; NE: not estimable; NS: not statistically significant; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

[a] Time from randomization to progression or death due to any cause, whichever occurs first. Cutoff date: 03 June 2011.

[b] Assessed by independent radiology review according to RECIST.

[c] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status and prior therapy.

[d] Cutoff date: 01 November 2011.

[e] Cutoff date: 31 August 2010.

[f] Risk ratio is used for ORR. A risk ratio > 1 indicated a higher likelihood of responding in the axitinib arm; a risk ratio < 1 indicated a higher likelihood of responding in the sorafenib arm.

[g] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior therapy.

[h] One-sided p-value from a log-rank test of treatment stratified by ECOG performance status.

[i] One-sided p-value from Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status.

Figure 1. Kaplan-Meier curve of progression-free survival by independent assessment for the overall population

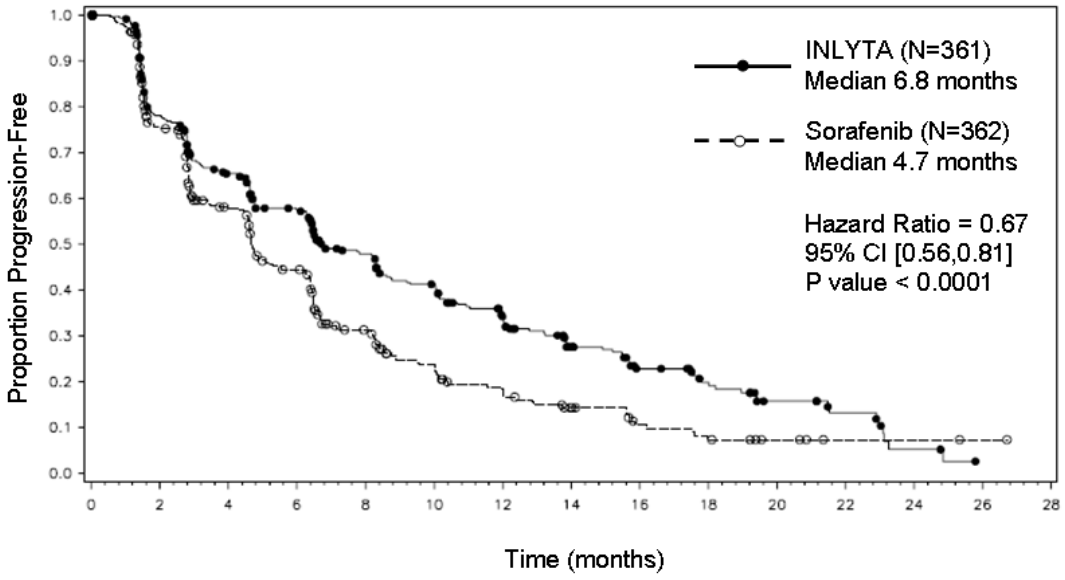


Figure 2. Kaplan-Meier curve of progression-free survival by independent assessment for the prior sunitinib subgroup

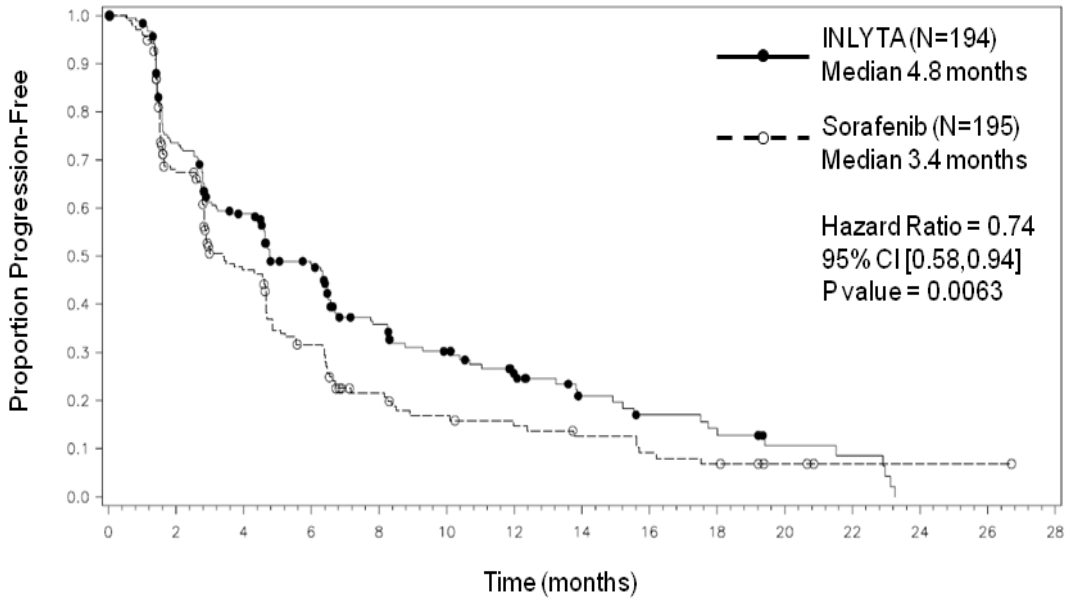
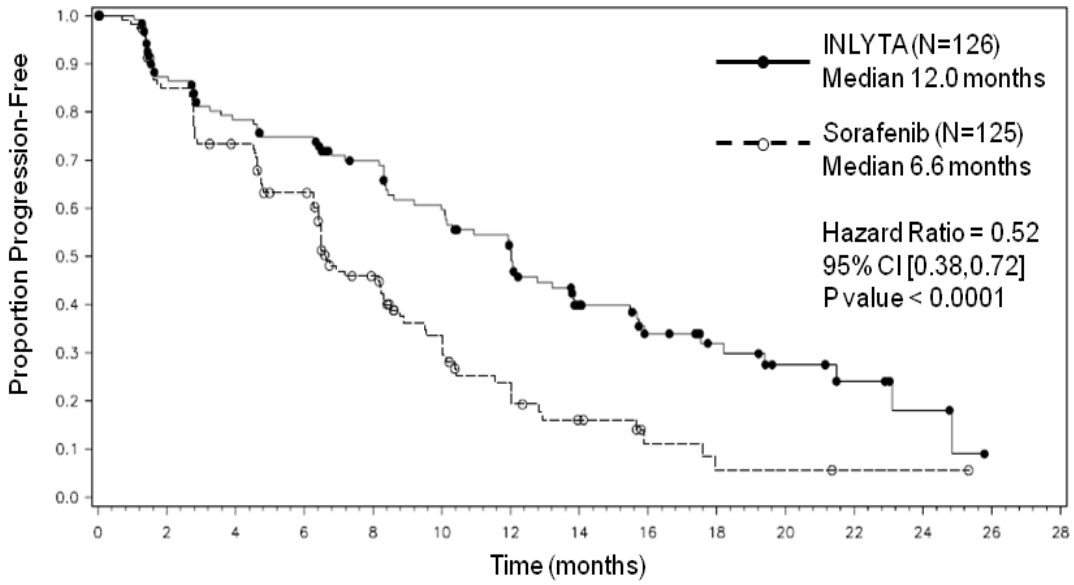


Figure 3. Kaplan-Meier curve of progression-free survival by independent assessment for the prior cytokine subgroup



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with axitinib in all subsets of the paediatric population for treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

After oral administration of axitinib tablets, the mean absolute bioavailability is 58% compared to intravenous administration. The plasma half life of axitinib ranges from 2.5 to 6.1 hours. Dosing of axitinib at 5 mg twice daily resulted in less than two-fold accumulation compared to administration of a single dose. Based on the short half-life of axitinib, steady state is expected within 2 to 3 days of the initial dose.

Absorption and distribution

Peak axitinib concentrations in plasma are generally reached within 4 hours following oral administration of axitinib with median T_{max} ranging from 2.5 to 4.1 hours. Administration of axitinib with a moderate fat meal resulted in 10% lower exposure compared to overnight fasting. A high fat, high-calorie meal resulted in 19% higher exposure compared to overnight fasting. Axitinib may be administered with or without food (see section 4.2).

The average C_{max} and AUC increased proportionally over an axitinib dosing range of 5 to 10 mg. *In vitro* binding of axitinib to human plasma proteins is > 99% with preferential binding to albumin and moderate binding to α_1-acid glycoprotein. At the 5 mg twice daily dose in the fed state, the geometric mean peak plasma concentration and 24-hour AUC were 27.8 ng/ml and 265 ng.h/ml, respectively, in patients with advanced RCC. The geometric mean oral clearance and apparent volume of distribution were 38 L/h and 160 L, respectively.

Biotransformation and elimination

Axitinib is metabolised primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

Following oral administration of a 5 mg radioactive dose of axitinib, 30-60% of the radioactivity was recovered in faeces and 23% of the radioactivity was recovered in urine. Unchanged axitinib, accounting for 12% of the dose, was the major component identified in faeces. Unchanged axitinib was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged axitinib and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity.

The sulfoxide and N-glucuronide metabolites show approximately 400-fold and 8000-fold less *in vitro* potency, respectively, against VEGFR-2 compared to axitinib.

Special populations

Elderly patients, gender, and race

Population pharmacokinetic analyses in patients with advanced cancer (including advanced RCC) and healthy volunteers indicate that there are no clinically relevant effects of age, gender, body weight, race, renal function, UGT1A1 genotype, or CYP2C19 genotype.

Paediatric population

Axitinib has not been studied in patients < 18 years of age.

Hepatic impairment

In vitro and *in vivo* data indicate that axitinib is primarily metabolised by the liver.

Compared to subjects with normal hepatic function, systemic exposure following a single dose of axitinib was similar in subjects with mild hepatic impairment (Child-Pugh class A) and higher (approximately two-fold) in subjects with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and should not be used in this population (see section 4.2 for dose adjustment recommendations).

Renal impairment

Unchanged axitinib is not detected in the urine.

Axitinib has not been studied in subjects with renal impairment. In clinical studies with axitinib for the treatment of patients with RCC, patients with serum creatinine > 1.5 times the ULN or calculated creatinine clearance < 60 ml/min were excluded. Population pharmacokinetic analyses have shown that axitinib clearance was not altered in subjects with renal impairment and no dose adjustment of axitinib is required.

5.3 Preclinical safety data

Repeat dose toxicity

Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were the gastrointestinal, haematopoietic, reproductive, skeletal and dental systems, with No Observed Adverse Effect Levels (NOAEL) approximately equivalent to or below expected human exposure at the recommended clinical starting dose (based on AUC levels).

Carcinogenicity

Carcinogenicity studies have not been performed with axitinib.

Genotoxicity

Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays *in vitro*. A significant increase in polyploidy was observed *in vitro* at concentrations > 0.22 µg/ml, and an elevation in micronucleated polychromatic erythrocytes was observed *in vivo* with No Observed Effect Level (NOEL) 69-fold the expected human exposure. Genotoxicity findings are not considered clinically relevant at exposure levels observed in humans.

Reproduction toxicity

Axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. These findings were observed in mice at exposure levels approximately 12-fold the expected human exposure, and in dogs at exposure levels below the expected human exposure. There was no effect on mating or fertility in male mice at exposure levels approximately 57-fold the expected human exposure. Findings in females included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice at all doses tested, with exposure levels at the lowest dose approximately 10-fold the expected human exposure.

Pregnant mice exposed to axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, at exposure levels below the expected human exposure. Perinatal and postnatal developmental toxicity studies have not been conducted.

Toxicity findings in immature animals

Reversible physeal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately six-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for more than 1 month at exposure levels similar to the expected human exposure. Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Magnesium stearate

Film-coating:

Hypromellose

Titanium dioxide (E171)

Lactose monohydrate

Triacetin (E1518)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister. Each pack contains 28 or 56 tablets.

HDPE bottle with a silica gel desiccant and a polypropylene closure containing 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich, Kent CT13 9NJ

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

10.2 Appendix 2: Search strategy for Section 6.1 (Identification of studies)

10.2.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (Ovid)
- The Cochrane Library
- Web of Science

10.2.2 *The date on which the search was conducted*

The searches were originally conducted on 1 July 2010 and updated on 27 April 2012.

10.2.3 *The date span of the search*

- Ovid MEDLINE(R) 1946 to present.
- EMBASE (Ovid), 1974 to 2012 April 26.
- The Cochrane Library, to present.

10.2.4 *The complete search strategy used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

The following searches were combined and inclusion/exclusion criteria applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present.; Searched on July 1st 2010 updated on 27 April 2012

# ▲	Searches	Results
1	exp Carcinoma, Renal Cell/	17067
2	exp Kidney Neoplasms/	48454
3	((renal or kidney) adj3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	55444

4	(sunitinib or su?10398 or su ?10398 or sutent).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1219
5	(temsirolimus or cci 779 or cci779 or nsc 683864 or nsc683864 or torisel).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	510
6	(sorafenib or bay 439006 or bay439006 or nexavar).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1298
7	(bevacizumab or nsc 704865 or nsc704865 or avastin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3908
8	Protein Kinase Inhibitors/ad, tu, to [Administration & Dosage, Therapeutic Use, Toxicity]	3400
9	(pazopanib or armala or gw 786034* or gw786034* or sb710468* or sb 710468*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	98
10	(hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1203
11	(everolimus or certican or rad001* or rad 001*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1106
12	(axitinib or ag13736 or ag 13736).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	100
13	exp Interleukin-2/	32938
14	(interleukin 2 or bioleukin or IL-2).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	62491
15	exp Interferon-alpha/	19938
16	((alpha adj2 interferon) or alferon or cilferon or kemron or veldona).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	26798
17	Randomized controlled trials as Topic/	67897
18	Randomized controlled trial/	293989

19	Random allocation/	68909
20	Double blind method/	107210
21	Single blind method/	14120
22	Clinical trial/	463119
23	exp Clinical Trials as Topic/	230170
24	or/17-23	744869
25	(clinic$ adj trial$1).tw.	149920
26	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	106594
27	Placebos/	28991
28	Placebo$.tw.	127362
29	Randomly allocated.tw.	12462
30	(allocated adj2 random).tw.	657
31	or/25-30	318213
32	24 or 31	845505
33	Case report.tw.	158127
34	Letter/	696207
35	Historical article/	265237
36	Review of reported cases.pt.	0
37	Review, multicase.pt.	0

38	or/33-37	1110245
39	32 not 38	821654
40	Meta-Analysis as Topic/	10370
41	meta analy$.tw.	30827
42	metaanaly$.tw.	967
43	Meta-Analysis/	25239
44	(systematic adj (review$1 or overview$1)).tw.	23928
45	exp Review Literature as Topic/	4933
46	or/40-45	64681
47	cochrane.ab.	15093
48	embase.ab.	12529
49	(psychlit or psyclit).ab.	820
50	(psychinfo or psycinfo).ab.	3825
51	(cinahl or cinhal).ab.	4815
52	science citation index.ab.	1188
53	bids.ab.	292
54	cancerlit.ab.	481
55	or/47-54	23346
56	reference list$.ab.	5707

57	bibliograph$.ab.	8757
58	hand-search$.ab.	2518
59	relevant journals.ab.	433
60	manual search$.ab.	1436
61	or/56-60	16916
62	selection criteria.ab.	13263
63	data extraction.ab.	6358
64	62 or 63	18586
65	Review/	1535659
66	64 and 65	12180
67	Comment/	435264
68	Letter/	696207
69	Editorial/	266516
70	animal/	4590221
71	human/	11286642
72	70 not (70 and 71)	3409981
73	or/67-69,72	4417487
74	46 or 55 or 61 or 66	84170
75	74 not 73	78029

76	(euroqol or eq5d or eq 5d or eqvas or eq vas).mp.	1973
77	(sf36 or sf 36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36 or shortform36).mp.	10507
78	(sf6D or sf 6D or sf sixD or sf six D or short form 6D or short form six D or shortform 6D or shortform6D).mp.	194
79	(sf12 or sf 12 or sf twelve or short form 12 or short form twelve).mp.	1474
80	(hql or hrqol or qol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	15352
81	(quality of life or life quality or quality of wellbeing or quality of well being or quality adjusted life or qaly).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	132097
82	((health* and year* and equivalent*) or hye).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	3733
83	(health utilit* or hui or health preference*).mp.	1073
84	health utility index.mp.	71
85	(visual analog* scale or VAS).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	29910
86	((persontradeoff or person tradeoff or person trade off or person trade* or health) adj2 (status or standard gamble* or timetradeoff or time tradeoff or time trade off or time trade*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	77604
87	(TTO or time trade off or standard gamble or SG).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	5026
88	exp "Quality of Life"/	83492
89	exp Quality-Adjusted Life Years/	4428
90	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89	232221

91	1 or 2 or 3 or 10	57759
92	4 or 5 or 6 or 7 or 8 or 9 or 11 or 12 or 13 or 14 or 15 or 16	100350
93	39 or 75 or 90	1057682
94	91 and 92 and 93	1408
95	limit 94 to yr="2000 -Current"	852

EMBASE 1980 to 2010 Week 25; Searched on July 1st 2010 updated on 27 April 2012

# ▲	Searches	Results
1	exp kidney carcinoma/	23780
2	exp kidney tumor/	44492
3	((renal or kidney) adj3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	46702
4	(hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	522
5	exp sunitinib/	4407
6	(sunitinib or su?10398 or su ?10398 or sutent).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	4457
7	exp temsirolimus/	2229
8	(temsirolimus or cci 779 or cci779 or nsc 683864 or nsc683864 or torisel).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device	2272

	manufacturer, drug manufacturer name]	
9	exp sorafenib/	4773
10	(sorafenib or bay 439006 or bay439006 or nexavar).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	4835
11	exp bevacizumab/	11650
12	(bevacizumab or nsc 704865 or nsc704865 or avastin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	11805
13	exp protein kinase inhibitor/ae, ct, ad, dt, to [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Therapy, Drug Toxicity]	39334
14	exp pazopanib/	586
15	(pazopanib or armala or gw 786034* or gw786034* or sb710468* or sb 710468*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	593
16	exp everolimus/	3519
17	(everolimus or certican or rad001* or rad 001*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	3597
18	exp axitinib/	648
19	(axitinib or ag13736 or ag 13736).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	663
20	exp interleukin 2/	47299
21	(interleukin 2 or bioleukin or IL-2).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	73675
22	exp alpha interferon/	33016

23	((alpha adj2 interferon) or alferon or cilferon or kemron or veldona).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	44053
24	Clinical trial/	603412
25	Randomized controlled trial/	190745
26	Randomization/	28445
27	Single blind procedure/	9578
28	Double blind procedure/	78393
29	Crossover procedure/	23179
30	Placebo/	143812
31	Randomi?ed controlled trial$.tw.	40867
32	Rct.tw.	3621
33	Random allocation.tw.	699
34	Randomly allocated.tw.	11244
35	Allocated randomly.tw.	1416
36	(allocated adj2 random).tw.	575
37	Single blind$.tw.	8202
38	Double blind$.tw.	90865
39	((treble or triple) adj blind$).tw.	153
40	Placebo$.tw.	119887

41	Prospective study/	96561
42	or/24-41	792468
43	Case study/	7253
44	Case report.tw.	133278
45	Abstract report/ or letter/	542144
46	or/43-45	679916
47	42 not 46	765228
48	exp Meta Analysis/	38801
49	((meta adj analy$) or metaanalys$).tw.	29071
50	(systematic adj (review$1 or overview$1)).tw.	21259
51	or/48-50	66222
52	cancerlit.ab.	370
53	cochrane.ab.	10784
54	embase.ab.	9407
55	(psychlit or psyclit).ab.	483
56	(psychinfo or psycinfo).ab.	2284
57	(cinahl or cinhal).ab.	2976
58	science citation index.ab.	869
59	bids.ab.	214

60	or/52-59	16779
61	reference lists.ab.	3568
62	bibliograph$.ab.	6914
63	hand-search$.ab.	1711
64	manual search$.ab.	1202
65	relevant journals.ab.	312
66	or/61-65	12370
67	data extraction.ab.	6431
68	selection criteria.ab.	8249
69	67 or 68	14202
70	review.pt.	1036160
71	69 and 70	8180
72	letter.pt.	489651
73	editorial.pt.	258797
74	animal/	54642
75	human/	7088044
76	74 not (74 and 75)	38072
77	or/72-73,76	786020
78	51 or 60 or 66 or 71	81378

79	78 not 77	77368
80	(euroqol or eq5d or eq 5d or eqvas or eq vas).mp.	1854
81	(sf36 or sf 36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36 or shortform36).mp.	11149
82	(sf6D or sf 6D or sf sixD or sf six D or short form 6D or short form six D or shortform 6D or shortform6D).mp.	187
83	(sf12 or sf 12 or sf twelve or short form 12 or short form twelve).mp.	1410
84	(hql or hrqol or qol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	14085
85	(quality of life or life quality or quality of wellbeing or quality of well being or quality adjusted life or qaly).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	134982
86	((health* and year* and equivalent*) or hye).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	3360
87	(health utilit* or hui or health preference*).mp.	1276
88	health utility index.mp.	66
89	(visual analog* scale or VAS).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	31935
90	((persontradeoff or person tradeoff or person trade off or person trade* or health) adj2 (status or standard gamble* or timetradeoff or time tradeoff or time trade off or time trade*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	49861
91	(TTO or time trade off or standard gamble or SG).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	4492
92	exp "quality of life"/	119411

93	80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92	214789
94	1 or 2 or 3 or 4	53780
95	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	154627
96	47 or 79 or 93	954118
97	94 and 95 and 96	3557
98	limit 97 to yr="2000 -Current"	3140

The Cochrane Library, to present; Searched on July 1st 2010 updated on 27 April 2012

ID	Search	Hits
#1	MeSH descriptor **Carcinoma, Renal Cell** explode all trees	326
#2	MeSH descriptor **Kidney Neoplasms** explode all trees	508
#3	(renal or kidney) NEAR/3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)	947
#4	hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*	7
#5	sunitinib or su?10398 or su ?10398 or sutent	55
#6	temsirolimus or cci 779 or cci779 or nsc 683864 or nsc683864 or torisel	34
#7	sorafenib or bay 439006 or bay439006 or nexavar	86
#8	bevacizumab or nsc 704865 or nsc704865 or avastin	300
#9	MeSH descriptor **Protein Kinase Inhibitors** explode all trees	207
#10	pazopanib or armala or gw 786034* or gw786034* or sb710468* or sb 710468*	8
#11	everolimus or certican or rad001* or rad 001*	697
#12	axitinib or ag13736 or ag 13736	7

#13	MeSH descriptor **Interleukin-2** explode all trees	725
#14	interleukin 2 or bioleukin or IL-2	5982
#15	MeSH descriptor **Interferon-alpha** explode all trees	2166
#16	(alpha NEAR/2 interferon) or alferon or cilferon or kemron or veldona	3162
#17	(#1 OR #2 OR #3 OR #4)	964
#18	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)	10858
#19	(#17 AND #18)	352
#20	(#19), from 2000 to 2010	191

Web of science

72	(RENAL OR KIDNEY) NEAR (CARCINOMA$1 OR ADENOCARCINOMA$1 OR CANCER$5 OR NEOPLASM$4 OR TUMOUR$4 OR TUMOR$4)	29749
73	SUNITINIB OR SU-10398 OR SU10398 OR SUTENT	1558
74	TEMSIROLIMUS OR CCI-779 OR CCI779 OR NSC-683864 OR NSC683864 OR TORISEL	539
75	SORAFENIB OR BAY-439006 OR BAY439006 OR NEXAVAR	1659
76	BEVACIZUMAB OR NSC-704865 OR NSC704865 OR AVASTIN	5098
77	PROTEIN ADJ KINASE ADJ INHIBITOR$1	3108
78	PAZOPANIB OR ARMALA OR GW-786034$ OR GW786034$ OR SB710468$ OR SB-710468$	112
79	HYPERNEPHROMA$ OR NEPHROID ADJ CARCINOMA$1 OR HYPEMEPHROID ADJ CARCINOMA$1	113
80	EVEROLIMUS OR CERTICAN OR RAD001$ OR RAD-001$	1555
81	AXITINIB OR AG13736 OR AG-13736	97
82	INTERLEUKIN-2 OR INTERLEUKIN ADJ '2' OR BIOLEUKIN OR IL-2 OR IL2	20041

83	ALPHA NEAR INTERFERON OR ALFERON OR CILFERON OR KEMRON OR VELDONA	25027
84	CLINIC$4 ADJ TRIAL$1 OR CLINIC$4 ADJ STUD$4	174733
85	(SINGL$2 OR DOUBL$2 OR TREB$2 OR TRIPL$2) ADJ (BLIND$3 OR MASK$3)	106303
86	PLACEBO$1	105201
87	RANDOM$5 ADJ ALLOCAT$5	8464
88	CROSSOVER ADJ (PROCEDURE$1 OR TRIAL$1 OR STUD$3)	10005
89	(RANDOMIS$6 OR RANDOMIZ$6) ADJ CONTROL$3 ADJ (TRIAL$1 OR STUD$3)	84513
90	PROSPECTIVE ADJ (TRIAL$1 OR STUD$3)	65197
91	META ADJ ANALY$3 OR METANALY$3	29808
92	SYSTEMATIC ADJ (REVIEW$2 OR OVERVIEW$2)	26340
93	(CASE ADJ REPORT).PT.	0
94	LETTER.PT.	545626
95	EDITORIAL.PT.	771389
96	(HISTORICAL ADJ ARTICLE).PT.	0
97	(CASE ADJ REPORT).DT.	87579
98	LETTER.DT.	1072891
99	EDITORIAL.DT.	837365
100	(HISTORICAL ADJ ARTICLE).DT.	68
101	SF36 OR SF-36 OR SF ADJ THIRTYSIX OR SF ADJ THIRTY ADJ SIX OR SHORT ADJ FORM ADJ '36' OR SHORT ADJ FORM ADJ THIRTY ADJ SIX OR SHORT ADJ FORM ADJ THIRTYSIX OR SHORTFORM ADJ '36' OR SHORTFORM36	5836
102	SF6D OR SF ADJ 6D OR SF ADJ SIXD OR SF ADJ SIX ADJ D OR SHORTFORM ADJ 6D OR SHORT ADJ FORM ADJ 6D OR SHORTFORM ADJ SIX ADJ D OR SHORT ADJ FORM ADJ SIX ADJ D	233

103	SF12 OR SF ADJ '12' OR SF ADJ TWELVE OR SHORTFORM ADJ '12' OR SHORT ADJ FORM ADJ '12' OR SHORTFORM ADJ TWELVE OR SHORT ADJ FORM ADJ TWELVE	1296
104	HQL OR HRQOL OR QOL	13386
105	QUALITY ADJ OF ADJ LIFE OR LIFE ADJ QUALITY OR QUALITY ADJ OF ADJ WELLBEING OR QUALITY ADJ OF ADJ WELL ADJ BEING OR QUALITY ADJ ADJUSTED ADJ LIFE OR QALY	53013
106	HEALTH$4 AND YEAR$3 AND EQUIVALEN$4 OR HYE	9260
107	HEALTH ADJ UTILIT$4 OR HUI OR HEALTH ADJ PREFERENCE$2	38625
108	HEALTH ADJ UTILITY ADJ INDEX	502
109	VISUAL ADJ ANALOG$3 ADJ SCALE OR VAS	27795
110	(PERSONTRADEOFF OR PERSON ADJ TRADEOFF OR PERSON ADJ TRADE$1 ADJ OFF OR PERSON ADJ TRADE$2 OR HEALTH) NEAR (STATUS OR STANDARD ADJ GAMBLE$2 OR TIMETRADEOFF OR TIME ADJ TRADEOFF OR TIME ADJ TRADE$1 ADJ OFF OR TIME ADJ TRADE$3)	24509
111	TTO OR TIME ADJ TRADE ADJ OFF OR STANDARD ADJ GAMBLE OR SG	41231
112	COCHRANE.AB.	10160
113	EMBASE.AB.	9113
114	(PSYCHLIT OR PSYCLIT).AB.	410
115	(PSYCHINFO OR PSYCINFO).AB.	2129
116	(CINAHL OR CINHAL).AB.	3342
117	CANCERLIT.AB.	326
118	(REFERENCE ADJ LIST$).AB.	299
119	(REFERENCE ADJ LIST$2).AB.	4072
120	BIBLIOGRAPH$4.AB.	7187
121	HAND-SEARCH$2.AB.	0
122	(RELEVANT ADJ JOURNAL$1).AB.	297

123	(MANUAL ADJ SEARCH$2).AB.	953
124	(SELECTION ADJ CRITERIA).AB.	9646
125	(DATA ADJ EXTRACTION).AB.	4760
126	COMMENT.PT,DT.	0
127	LETTER.PT,DT.	545626
128	72 OR 79	29794
129	73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 80 OR 81 OR 82 OR 83	55021
130	84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90	420854
131	93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100	1982790
132	130 NOT 131	394667
133	91 OR 92	48614
134	112 OR 113 OR 114 OR 115 OR 116 OR 117	15233
135	118 OR 119 OR 120 OR 121 OR 122 OR 123 OR 124 OR 125	22840
136	126 OR 127	545626
137	132 NOT 136	394667
138	101 OR 102 OR 103 OR 104 OR 105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111	191283
139	133 OR 134 OR 135 OR 137 OR 138	600007
140	128 AND 129 AND 139	888
141	YEAR=2010 OR YEAR=2009 OR YEAR=2008 OR YEAR=2007 OR YEAR=2006 OR YEAR=2005 OR YEAR=2004 OR YEAR=2003 OR YEAR=2002 OR YEAR=2001 OR YEAR=2000	12536138
142	140 AND 141	778

10.2.5 *Details of any additional searches, such as searches of company databases (include a description of each database).*

Hand searching of conference proceedings for the American Society of Clinical Oncology (including the Genito-Urinary symposium), the European Society for Medical Oncology

and the European Cancer Organisation was conducted. The Food and Drugs Administration website was also searched for Oncologic Drugs Advisory Committee reports. Clinical study reports were provided by the manufacturer.

10.2.6 *The inclusion and exclusion criteria.*

	Description	Justification
Inclusion criteria		
Population	Adult patients with metastatic RCC who have received first- or second-line treatment.	As specified by final scope
Interventions	Any chemotherapy or targeted therapy in the second-line setting.	In addition to the final scope, other interventions (both first and second-line) were searched in the systematic review. Studies with first-line treatment were later excluded for the purpose of this submission. Only the relevant comparator studies were selected for the indirect comparison.
Outcomes	**Efficacy** • Overall survival (OS) • Progression-free survival (PFS) • Time to progression (TTP) • Overall response rate (complete + partial response) • Proportion of patients with stable disease • Duration of response • Time to response • Symptom assessments (where reported) • Time to deterioration (composite/individual endpoint) **Safety** Incidence and severity of adverse events (AEs) including, but not restricted to: • Incidence and severity (grade) of all reported AEs, e.g. hypertension • Withdrawals due to AEs • Incidence of serious AEs Quality of life or any other global patient-reported outcomes	Consistent with final scope with the exception that studies were not filtered for health-related quality of life
Study design	Prospective randomised controlled trials	Non-RCT studies were identified through a separate search
Language restrictions	English language only	To reduce the number of hits
Exclusion criteria		

	Description	Justification
Population	Subjects <18 years of age	As specified by final scope
Interventions	Radiotherapy, surgery and other non-relevant comparators	Not relevant to final scope
Outcomes	Studies not investigating efficacy, safety or QoL	Not relevant to final scope
Study design	Non-RCT	Non-RCT studies were identified through a separate search
Language restrictions	Abstracts published in non-English language	

10.2.7 *The data abstraction strategy.*

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 *A suggested format for the quality assessment of RCT(s) is shown below.*

AXIS trial (A4061032)		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Randomisation lists were generated from an independent randomisation group using a permuted block design of size four (two to axitinib and two to sorafenib) within each stratum.	Yes
Was the concealment of treatment allocation adequate?	A web-enabled centralised registration system concealed treatment allocation before registration and allowed centres to enrol patients directly.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Demographics and baseline characteristics were typical of a population with advanced renal cell carcinoma and were well balanced between the axitinib and sorafenib groups (presented in table).	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients and investigators were not masked to study treatment. Progression-free survival and objective response rate were assessed by a masked independent radiology review.	No, low risk of bias. PFS and ORR were assessed blinded.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	In the axitinib arm, 221/361 discontinued treatment (160 due to disease progression/relapse) and in the sorafenib arm, 256/362 discontinued treatment (180 due to disease progression). There were no imbalances for drop-outs between groups for efficacy or safety analyses.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy was assessed in the intention-to-treat population. Duration of response was assessed using descriptive statistics. Symptom deterioration was assessed in the intention-to-treat population. All patients receiving treatment underwent safety analysis.	Yes, yes appropriate methods were used.

10.4 Appendix 4: Search strategy for Section 6.7 (Indirect and mixed treatment comparisons)

The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for comparator interventions, relevant to the decision problem.

10.4.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

N/A

10.4.2 *The date on which the search was conducted*

N/A

10.4.3 *The date span of the search*

N/A

10.4.4 *The complete search strategies used. including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

N/A

10.4.5 *Details of any additional searches, such as searches of company databases (include a description of each database).*

N/A

10.4.6 *The inclusion and exclusion criteria.*

N/A

10.4.7 *The data abstraction strategy.*

N/A

10.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 *A suggested format for the quality assessment of RCT(s) is shown below.*

TARGET		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Patients were stratified according to country and MSKCC prognostic score (favourable or intermediate) and randomly assigned to study groups in a 1:1 ratio with a block size of four.	Not clear
Was the concealment of treatment allocation adequate?	Not addressed	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Baseline characteristics were well balanced between the study groups (presented in table).	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The patients received either continuous treatment with oral sorafenib (at a dose of 400 mg twice daily) or placebo in a double-blind fashion, administered in 6-week cycles for the first 24 weeks and in 8-week cycles thereafter. Outcome analyses by independent review committee.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Of the 903 randomly assigned patients, 700 (78%) entered post-treatment follow-up at any time during the trial (337 [75%] from the sorafenib group and 363 [80%] from the placebo group). The most frequent reasons for discontinuation in the sorafenib and placebo groups were death (229 v 248 patients, respectively), loss to follow-up (8 vs 13 patients, respectively), and withdrawal of consent (6 vs 5 patients, respectively).There were no unexpected imbalances in drop-outs between groups for efficacy or safety analyses.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	No

TARGET		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All randomly assigned patients were included in the intent-to-treat (ITT) population for the efficacy analyses. All patients receiving at least one dose of sorafenib were eligible for the safety analysis. To account for a possible survival benefit after cross over, a pre-specified ITT survival analysis uniformly censoring patients originally randomly assigned to placebo at the time of cross-over was also conducted.	Yes, yes appropriate methods were used.

10.6 Appendix 6: Search strategy for Section 6.8 (Non-RCT evidence)

The clinical search described in 6.1 was also designed to identify eligible Non-RCT studies for axitinib.

10.6.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- EMBASE (Ovid)
- The Cochrane Library

10.6.2 *The date on which the search was conducted.*

The searches were conducted on April 24th 2012

10.6.3 *The date span of the search.*

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present Search strategy
- Embase 1974 to 2012 April 23
- The Cochrane Library, to present.

10.6.4 *The complete search strategies used. including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: accessed April 24th 2012

# ▲	Searches	Results
1	exp Carcinoma, Renal Cell/	19312
2	exp Kidney Neoplasms/	52235
3	((renal or kidney) adj3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique	60727

	identifier]	
4	(hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1228
5	(axitinib or ag13736 or ag 13736).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	156
6	Epidemiologic studies/	5315
7	exp case control studies/	545798
8	exp cohort studies/	1163464
9	Case control.tw.	62206
10	(cohort adj (study or studies)).tw.	62814
11	Cohort analy$.tw.	2824
12	(Follow up adj (study or studies)).tw.	33639
13	(observational adj (study or studies)).tw.	32542
14	Longitudinal.tw.	115144
15	Retrospective.tw.	220419
16	Cross sectional.tw.	128665
17	Cross-sectional studies/	138035
18	phase II.mp.	45578
19	or/6-18	1627660

20	1 or 2 or 3 or 4	63154
21	5 and 19 and 20	19

Embase 1974 to 2012 April 23: accessed April 24th 2012

# ▲	Searches	Results
1	exp kidney carcinoma/	37786
2	exp kidney tumor/	82346
3	((renal or kidney) adj3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	87816
4	(hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1506
5	exp axitinib/	1111
6	(axitinib or ag13736 or ag 13736).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1146
7	Clinical study/	83114
8	Case control study/	66288
9	Family study/	9543
10	Longitudinal study/	52106
11	Retrospective study/	275783
12	Prospective study/	201344

13	Randomized controlled trials/	15101
14	12 not 13	200973
15	Cohort analysis/	120848
16	(Cohort adj (study or studies)).mp.	81306
17	(Case control adj (study or studies)).tw.	60574
18	(follow up adj (study or studies)).tw.	41549
19	(observational adj (study or studies)).tw.	43455
20	(epidemiologic$ adj (study or studies)).tw.	66033
21	(cross sectional adj (study or studies)).tw.	59926
22	phase II.mp.	47675
23	or/7-11,14-22	1007137
24	1 or 2 or 3 or 4	99892
25	5 or 6	1146
26	23 and 24 and 25	61

Cochrane Library: accessed April 24th 2012

ID	Search	Hits
#1	MeSH descriptor **Carcinoma, Renal Cell** explode all trees	393
#2	MeSH descriptor **Kidney Neoplasms** explode all trees	574
#3	(renal or kidney) NEAR/3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)	1135
#4	hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*	8
#5	axitinib or ag13736 or ag 13736	15
#6	(**#1** OR **#2** OR **#3** OR **#4**)	1152
#7	(#5 AND #6)	5

10.6.5 *Details of any additional searches, such as searches of company databases (include a description of each database).*

CSRs were provided by the manufacturer.

10.6.6 *The inclusion and exclusion criteria.*

	Description	Justification
Inclusion criteria		
Population	Adult patients with metastatic RCC who have received first- or second-line treatment.	As specified by final scope
Interventions	Any chemotherapy or targeted therapy in the second-line setting.	In addition to the final scope, other interventions (both first and second-line) were searched in the systematic review. Studies with first-line treatment were later excluded for the purpose of this submission. Only the relevant comparator studies were selected for the indirect comparison.

	Description	Justification
Outcomes	**Efficacy** • Overall survival (OS) • Progression-free survival (PFS) • Time to progression (TTP) • Overall response rate (complete + partial response) • Proportion of patients with stable disease • Duration of response • Time to response • Symptom assessments (where reported) • Time to deterioration (composite/individual endpoint) **Safety** Incidence and severity of adverse events (AEs) including, but not restricted to: • Incidence and severity (grade) of all reported AEs, e.g. hypertension • Withdrawals due to AEs • Incidence of serious AEs Quality of life or any other global patient-reported outcomes	Consistent with final scope
Study design	Non-RCT studies	Prospective randomised controlled trials were identified through a separate search
Language restrictions	English language only	
Exclusion criteria		
Population	Subjects <18 years of age	As specified by final scope
Interventions	Radiotherapy, surgery and other non-relevant comparators	Not relevant to final scope
Outcomes	Studies not investigating efficacy, safety or QoL	Not relevant to final scope
Study design	RCT	RCT studies were identified through a separate search
Language restrictions	Abstracts published in non-English language	

10.6.7 *The data abstraction strategy.*

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template by

a reviewer.

10.7 Appendix 7: Quality assessment of non-RCT(s) in Section 6.8 (Non-RCT evidence)

10.7.1 *Please tabulate the quality assessment of each of the non-RCTs identified.*

	Grade (yes/no/not clear/NA)		
Study question	**A4051035**	**A4061012**	**A4061023**
Were selection/eligibility criteria adequately reported?	Yes	Yes	Yes
Was the selected population representative of that seen in normal practice?	Yes	Yes	Yes
Was an appropriate measure of variability reported?	Yes	Yes	Yes[c]
Was loss to follow-up reported or explained?	Yes	Yes	Yes
Were at least 90% of those included at baseline followed up?	Yes	Yes	Yes
Were patients recruited prospectively?	Not clear, but given the Phase II design presumably so	Not clear, but given the Phase II design and reported accrual dates presumably so	Not clear, but given the Phase II design and reported accrual dates presumably so
Were patients recruited consecutively?	Not clear, but given the Phase II design presumably so	Not clear, but given the Phase II design and reported accrual dates presumably so	Not clear, but given the Phase II design and reported accrual dates presumably so
Did the study report relevant prognostic factors?	Yes	No, reported that absence of data precluded analysis of prognostic factors	No[d]

[c] Response definition stated in paper and definition of other outcomes reported in CSR.

[d] CSR reports: PK data in separate report and PD data not reported

10.8 Appendix 8: Search strategy for Section 6.9 (Adverse events)

The clinical search described in Section 6.1 and Section 10.2 was also designed to identify eligible studies for adverse events associated with axitinib and therefore a separate systematic review was not conducted.

10.8.1 ***The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:***

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

N/A

10.8.2 ***The date on which the search was conducted.***

N/A

10.8.3 ***The date span of the search.***

N/A

10.8.4 ***The complete search strategies used including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).***

N/A

10.8.5 ***Details of any additional searches, such as searches of company databases (include a description of each database).***

N/A

10.8.6 ***The inclusion and exclusion criteria.***

N/A

10.8.7 ***The data abstraction strategy.***

N/A

10.9 Appendix 9: Quality assessment of adverse event data in Section 6.9 (Adverse events)

10.9.1 *Please tabulate the quality assessment of each of studies identified.*

The quality assessment of studies reporting adverse event data are incorporated in Sections 10.3 and 10.7.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

10.10.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***EconLIT***
- ***NHS Economic Evaluation Database (NHS EED)***

The following databases were searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- Embase 1974 to 2012 June 08
- EconLIT 1961 to May 2012
- Cochrane Library: Health Technology Assessment 2nd Quarter 2012, NHS Economic Evaluation Database 2nd Quarter 2012

10.10.2 *The date on which the search was conducted.*

All searches were conducted on 11th June 2012.

10.10.3 *The date span of the search.*

All searches were conducted from 2006 - 11th June 2012.

Because the PenTAG report did not identify any relevant publications published prior to 2006, this year was chosen as cut-off year.

10.10.4 *The complete search strategies used, including all the search term textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

Embase 1974 to 2012 June 08, searched 11-06-2012

	Searches	Results
1	exp kidney metastasis/ or kidney metastas$.ab,ti.	1519
2	exp kidney carcinoma/ or (metastatic renal cell carcinoma or mrcc).ab,ti.	38637
3	renal cell neoplasm.ab,ti.	16
4	renal carcinoma.ab,ti.	4418
5	(renal cell cancer or renal cancer$).ab,ti.	6540
6	renal cell carcinoma.ab,ti.	24660

7	exp metastasis/ or metastas$.ab,ti.	405529
8	exp kidney/ or (renal or kidney).ab,ti.	832379
9	7 and 8	23507
10	1 or 2 or 3 or 4 or 5 or 6 or 9	56091
11	exp economics/ or exp health economics/	667486
12	exp "drug cost"/	51676
13	Socioeconomics/	101145
14	Cost benefit analysis/	60977
15	Cost effectiveness analysis/	80629
16	Cost of illness/	12961
17	Cost control/	41889
18	Financial management/	96210
19	Health care cost/	109870
20	Health care financing/	10776
21	Health economics/	31652
22	Hospital cost/	11924
23	(fiscal or financial or finance or funding).tw.	86186
24	Cost minimization analysis/	2060
25	(cost adj estimate$).mp.	1672
26	(cost adj variable$).mp.	135
27	(unit adj cost$).mp.	1935
28	exp economic evaluation/	185085
29	exp pharmacoeconomics/	153602
30	exp "cost utility analysis"/	4128

31	exp statistical model/ or exp hidden Markov model/	90423
32	exp "decision tree"/	4720
33	exp medical decision making/	60238
34	exp theoretical model/	55174
35	exp quality adjusted life year/	9164
36	exp economic aspect/	1004487
37	cost effectiveness analysis.sh. or randomized.tw. or economic.tw.	527747
38	cost$.tw.	388283
39	markov chains/	51473
40	Monte Carlo Method/	16966
41	exp Decision Theory/	1472
42	(pharmacoeconomic$ or pharmaco-economic$).mp.	9039
43	(cost$ effective$ or cost$ utilit$ or cost$ benefit$ or cost$ minimi$ or CEA or CUA or CMA).mp.	200646
44	(incremental cost effectiveness ratio or icer).mp.	3534
45	(decision$ tree$ or decision$ analy$ or decision$ model$ or markov model$).mp.	20195
46	exp Quality-Adjusted Life Years/	9164
47	(Quality-adjusted life year$ or QALY$).mp.	12192
48	or/11-47	1823388
49	exp axitinib/	1150
50	(axitinib or ag013736 or inlyta).tw.	268
51	exp tivozanib/	93
52	(tivozanib or av-951).tw.	85
53	exp pazopanib/	1514

54	(pazopanib or armala or gw786034 or sb710468).tw.	452
55	exp alpha interferon/	40739
56	(alpha-interferon or alfaferone or alferon or alpha ferone or cilferon or ginterferon or interferon-alpha or intropa or kemron or leukinferon or leukinferron or leukocyte interferon or refecon a or referon a3 or sumiferon or sumipheron or veldona).tw.	24235
57	(biotest or bioleukin or interleukin-ii or interleukin-2 or il-2 or il2 or ro-236019 or tcgf or tsf).tw.	67329
58	interleukin$.tw.	172719
59	exp sunitinib/	8841
60	(sunitinib or sutent or pha 2909040ad or pha2909040ad or "su 010398" or "su 011248" or su 10398 or su10398 or su 11248 or su010398 or su011248 or su11248).tw.	5612
61	exp sorafenib/	9918
62	(sorafenib bay 43-9006 or bay 439006 or bay43-9006 or bay439006 or nexavar).tw.	2158
63	exp everolimus/	7900
64	(everolimus or afinitor or certican or nvp-rad-001 or rad-001 or rad 001a or rad001 or rad001a or sdz rad).tw.	5069
65	exp temsirolimus/	3768
66	(temsirolimus or cci-779 or cell-cycle-inhibitor-779 or nsc 683864 or nsc683864 or torisel).tw.	2454
67	exp bevacizumab/	21865
68	(bevacizumab or avastin or nsc 704865 or nsc704865 or anti-vegf or rhumab-vegf).tw.	14666
69	or/49-68	283770
70	10 and 48 and 69	1498
71	limit 70 to (english and yr="2006 -Current")	1130

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1946 to Present, searched 11-06-2012

	Searches	Results
1	kidney metastas$.ab,ti.	60
2	exp Carcinoma, Renal Cell/ or (metastatic renal cell carcinoma or mrcc).ab,ti.	20124
3	renal cell neoplasm.ab,ti.	12
4	renal carcinoma.ab,ti.	3557
5	(renal cell cancer or renal cancer$).ab,ti.	4980
6	renal cell carcinoma.ab,ti.	18611
7	exp Neoplasm Metastasis/ or metastas$.ab,ti.	274537
8	exp kidney/ or (renal or kidney).ab,ti.	669540
9	7 and 8	14647
10	1 or 2 or 3 or 4 or 5 or 6 or 9	35571
11	Economics/	26316
12	"costs and cost analysis"/	39795
13	Cost allocation/	1917
14	Cost-benefit analysis/	54133
15	Cost control/	19188
16	Cost savings/	7610
17	Cost of illness/	15112
18	Cost sharing/	1740
19	"deductibles and coinsurance"/	1336
20	Medical savings accounts/	460
21	Health care costs/	23183
22	Direct service costs/	965

23	Drug costs/	11046
24	Employer health costs/	1042
25	Hospital costs/	6847
26	Health expenditures/	12393
27	Capital expenditures/	1911
28	Value of life/	5218
29	exp economics, hospital/	17944
30	exp economics, medical/	13280
31	Economics, nursing/	3862
32	Economics, pharmaceutical/	2340
33	exp "fees and charges"/	25846
34	exp budgets/	11433
35	(low adj cost).mp.	19243
36	(high adj cost).mp.	6975
37	(health?care adj cost$).mp.	3273
38	(fiscal or funding or financial or finance).tw.	69357
39	(cost adj estimate$).mp.	1236
40	(cost adj variable).mp.	30
41	(unit adj cost$).mp.	1318
42	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	149459
43	(cost$ effective$ or cost$ utilit$ or cost$ benefit$ or cost$ minimi$ or CEA or CUA or CMA).mp.	116328
44	exp Models, Statistical/ or exp Markov Chains/ or exp Computer Simulation/ or exp Models, Theoretical/	1139757
45	exp Patient Simulation/	2511

46	exp Decision Trees/	8000
47	(incremental cost effectiveness ratio or icer).mp.	2279
48	cost$.tw.	303936
49	cost effectiveness analysis.sh. or randomized.tw.	261895
50	Monte Carlo Method/	16961
51	exp Decision Theory/	8784
52	(decision$ tree$ or decision$ analy$ or decision$ model$ or markov model$).mp.	18574
53	exp Quality-Adjusted Life Years/	5682
54	(Quality-adjusted life year$ or QALY$).mp.	8252
55	or/11-54	1943493
56	(axitinib or ag013736 or inlyta).tw.	135
57	(tivozanib or av-951).tw.	11
58	(pazopanib or armala or gw786034 or sb710468).tw.	247
59	(alpha-interferon or alfaferone or alferon or alpha ferone or cilferon or ginterferon or interferon-alpha or intropa or kemron or leukinferon or leukinferron or leukocyte interferon or refecon a or referon a3 or sumiferon or sumipheron or veldona).tw.	20233
60	(biotest or bioleukin or interleukin-ii or interleukin-2 or il-2 or il2 or ro-236019 or tcgf or tsf).tw.	57523
61	interleukin$.tw.	151628
62	(sunitinib or sutent or pha 2909040ad or pha2909040ad or "su 010398" or "su 011248" or su 10398 or su10398 or su 11248 or su010398 or su011248 or su11248).tw.	2027
63	(sorafenib bay 43-9006 or bay 439006 or bay43-9006 or bay439006 or nexavar).tw.	143
64	(everolimus or afinitor or certican or nvp-rad-001 or rad-001 or rad 001a or rad001 or rad001a or sdz rad).tw.	1727
65	(temsirolimus or cci-779 or cell-cycle-inhibitor-779 or nsc 683864 or nsc683864 or torisel).tw.	659

66	(bevacizumab or avastin or nsc 704865 or nsc704865 or anti-vegf or rhumab-vegf).tw.	7175
67	or/56-66	200481
68	10 and 55 and 67	514
69	limit 68 to (yr="2006 -Current" and english)	283

Cochrane Library: Health Technology Assessment 2nd Quarter 2012, **NHS Economic Evaluation Database** 2nd Quarter 2012, searched 11-06-2012

	Searches	Results
1	kidney metastas$.ab,ti.	0
2	exp Carcinoma, Renal Cell/ or (metastatic renal cell carcinoma or mrcc).ab,ti.	54
3	renal cell neoplasm.ab,ti.	0
4	renal carcinoma.ab,ti.	1
5	(renal cell cancer or renal cancer$).ab,ti.	10
6	renal cell carcinoma.ab,ti.	45
7	exp Neoplasm Metastasis/ or metastas$.ab,ti.	229
8	exp kidney/ or (renal or kidney).ab,ti.	380
9	7 and 8	11
10	1 or 2 or 3 or 4 or 5 or 6 or 9	65
11	Economics/	19
12	"costs and cost analysis"/	2145
13	Cost allocation/	13
14	Cost-benefit analysis/	8484
15	Cost control/	117
16	Cost savings/	433

17	Cost of illness/	497
18	Cost sharing/	5
19	"deductibles and coinsurance"/	1
20	Medical savings accounts/	0
21	Health care costs/	2113
22	Direct service costs/	111
23	Drug costs/	834
24	Employer health costs/	8
25	Hospital costs/	715
26	Health expenditures/	114
27	Capital expenditures/	3
28	Value of life/	114
29	exp economics, hospital/	863
30	exp economics, medical/	35
31	Economics, nursing/	7
32	Economics, pharmaceutical/	148
33	exp "fees and charges"/	223
34	exp budgets/	29
35	(low adj cost).mp.	147
36	(high adj cost).mp.	242
37	(health?care adj cost$).mp.	101
38	(fiscal or funding or financial or finance).tw.	8558
39	(cost adj estimate$).mp.	2052
40	(cost adj variable).mp.	6

41	(unit adj cost$).mp.	4343
42	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	13156
43	(cost$ effective$ or cost$ utilit$ or cost$ benefit$ or cost$ minimi$ or CEA or CUA or CMA).mp.	12482
44	exp Models, Statistical/ or exp Markov Chains/ or exp Computer Simulation/ or exp Models, Theoretical/	2854
45	exp Patient Simulation/	7
46	exp Decision Trees/	588
47	(incremental cost effectiveness ratio or icer).mp.	1344
48	cost$.tw.	14096
49	cost effectiveness analysis.sh. or randomized.tw.	2160
50	Monte Carlo Method/	268
51	exp Decision Theory/	596
52	(decision$ tree$ or decision$ analy$ or decision$ model$ or markov model$).mp.	3602
53	exp Quality-Adjusted Life Years/	2002
54	(Quality-adjusted life year$ or QALY$).mp.	3569
55	or/11-54	15275
56	(axitinib or ag013736 or inlyta).tw.	1
57	(tivozanib or av-951).tw.	1
58	(pazopanib or armala or gw786034 or sb710468).tw.	6
59	(alpha-interferon or alfaferone or alferon or alpha ferone or cilferon or ginterferon or interferon-alpha or introma or kemron or leukinferon or leukinferron or leukocyte interferon or refecon a or referon a3 or sumiferon or sumipheron or veldona).tw.	98
60	(biotest or bioleukin or interleukin-ii or interleukin-2 or il-2 or il2 or ro-236019 or tcgf or tsf).tw.	17
61	interleukin$.tw.	32

62	(sunitinib or sutent or pha 2909040ad or pha2909040ad or "su 010398" or "su 011248" or su 10398 or su10398 or su 11248 or su010398 or su011248 or su11248).tw.	29
63	(sorafenib bay 43-9006 or bay 439006 or bay43-9006 or bay439006 or nexavar).tw.	5
64	(everolimus or afinitor or certican or nvp-rad-001 or rad-001 or rad 001a or rad001 or rad001a or sdz rad).tw.	19
65	(temsirolimus or cci-779 or cell-cycle-inhibitor-779 or nsc 683864 or nsc683864 or torisel).tw.	10
66	(bevacizumab or avastin or nsc 704865 or nsc704865 or anti-vegf or rhumab-vegf).tw.	68
67	or/56-66	256
68	10 and 55 and 67	15
69	limit 68 to (english language and yr="2006 -Current")	14

Econlit 1961 to May 2012, searched 11-06-2012

	Searches	Results
1	kidney metastas$.ab,ti.	0
2	(metastatic renal cell carcinoma or mrcc).ab,ti.	0
3	renal cell neoplasm.ab,ti.	0
4	renal carcinoma.ab,ti.	0
5	(renal cell cancer or renal cancer$).ab,ti.	0
6	renal cell carcinoma.ab,ti.	2
7	metastas$.ab,ti.	8
8	(renal or kidney).ab,ti.	147
9	7 and 8	1
10	1 or 2 or 3 or 4 or 5 or 6 or 9	2

10.10.5 *Details of any additional searches, such as searches of company databases (include a description of each database).*

The following conferences were searched (for 2011-2012):

- American Society of Clinical Oncology (ASCO), including Genitourinary Symposium and Annual Meeting.
- European Cancer Organisation (ECCO) and European Society for Medical Oncology (ESMO).
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR), including Annual International Meeting, European Meeting and other meetings.

In addition, the following sources were searched:

- Cost Effectiveness Analysis Registrye, using the search terms “renal cell carcinoma” and “RCC”.
- The NICE website was searched for evidence review group reports, manufacturer submissions and other relevant documents for second-line RCC treatments.
- Reference lists of included publications and relevant reviews were hand searched.

10.10.6 *The inclusion and exclusion criteria.*

Criteria	Include	Exclude
Population	Adults with advanced or metastatic RCC	Paediatric populations and other indications
Intervention	Axitinib	First-line treatments and non-pharmaceutical interventions
Comparator	• Pazopanib • Sunitinib • Sorafenib • Interferon-α • Interleukin-2 • Everolimus • Temsirolimus • Bevacizumab in combination with interferon • Tivozanib	Other interventions not licensed in RCC and combination therapies.
Outcomes	Cost outcomes (e.g. total costs, costs per life year gained, costs per QALY gained, ICER, ICUR)	NA
Setting	Any	Not limited

[e]https://research.tufts-nemc.org/cear4/Default.aspx

Criteria	Include	Exclude
Study design	• Economic evaluations o Cost-benefit analysis o Cost-effectiveness analysis o Cost-utility analysis o Cost-minimisation analysis o Cost-consequence analysis	Cost studies
Language of publication	English (English abstracts of non-English publications will be included)	Non-English publications
Date of publication	2006 onwards 2011 onwards for conference abstracts	Publications published prior to 2006

Abbreviations: ICER, incremental cost-effectiveness ratio; ICER, incremental cost-utility ratio;QALY, quality adjusted life year; RCC, renal cell carcinoma.

10.10.7 *The data abstraction strategy.*

Data were extracted into the summary tables by a reviewer. Uncertainties were resolved following discussion with a second reviewer

10.10.8 *Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision prob lem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, appendix 10.*

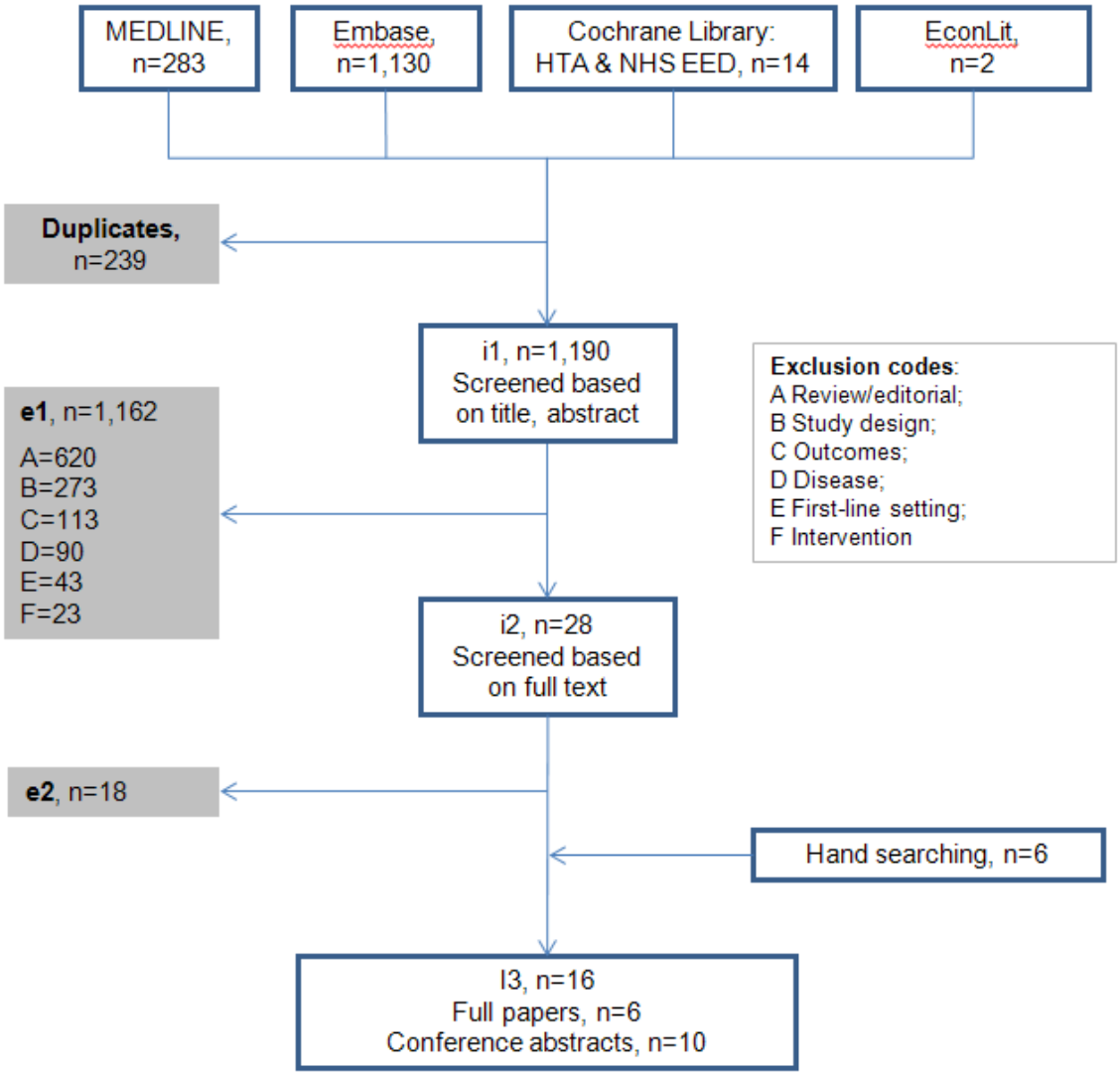
A systematic review was conducted to identify cost-effectiveness studies from the published literature for the treatment of advanced/mRCC after failure of prior systemic treatment.

The following electronic databases were searched; MEDLINE(R) In-Process and Other Non-Indexed Citations, Ovid MEDLINE(R), Embase, EconLIT, Cochrane Library: Health Technology Assessment 2nd Quarter 2012 and NHS Economic Evaluation Database 2nd Quarter 2012. Electronic searches were supplemented by hand searching the following sources; conference proceedings, the cost-effectiveness analysis (CEA) registry and NICE HTA submissions.

Full details of the databases, conference proceedings, search strategies employed and inclusion/exclusion criteria are presented in Section 10.10 (Appendix 10).

In total, 1,429 papers were identified through the electronic searches. Upon removal of duplicates, 1,190 titles and abstracts were reviewed. Of these, 28 records were reviewed based on full text, of which 18 were excluded, resulting in 10 records for final inclusion (six full publications and four conference abstracts). A further six records (six conference abstracts) were identified by hand searching.

Figure 42: Flow diagram for the systematic review of cost-effectiveness evaluations



10.10.9 ***Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided.***

Of the studies identified, 13 investigated the cost-effectiveness of an active therapy vs BSC in patients that had failed prior systemic treatment and provided a cost/QALY (114-126). Of the remaining three studies, one investigated the cost-effectiveness of an active comparator vs another active comparator and the remaining two did not report a cost/QALY.

Of the 13 studies that reported a cost/QALY with an active comparator vs BSC, three were conducted in the UK from the persepective of the NHS and were therefore considered the most relevant to the decision problem.

- Hoyle et al reported that compared to BSC, sorafenib treatment resulted in an incremental cost per QALY gained of £75,398, based on an estimated mean gain of 0.27 QALYs per patient (119)
- The ERG assessment of the cost-effectiveness analysis performed for the everolimus STA submission reported a cost/QALY of £65,231 for everolimus + BSC vs BSC alone (with a PAS scheme applied) compared with the cost/QALY of £51,613 for everolimus + BSC vs BSC alone (with a PAS scheme applied) sumbitted by the manufacturer
- Thompson-Coon et al reported a cost/QALY of £102,498 for sorafenib vs BSC.

These analyses conducted from a UK perspective highlight the challenges involved in attaining cost-effectiveness with second-line therapies for advanced/mRCC patients that have failed prior therapy.

A summary of the identified studies is presented in Table 67.

Table 67: Summary list of cost-effectiveness evaluations

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Aiello et al (114)	2007	Argentina	To estimate the cost-effectiveness of sunitinib malate versus BSC in the treatment of cytokine-refractory mRCC patients	Cytokine-refractory metastatic RCC patients failing on IL-2, IFN-alpha or combination of these.	Markov model. Effectiveness results and utility data were taken from a clinical trial and a US Medicare database. Data was adjusted with general population mortality estimates from Argentinean life tables.	Discounted: 0.98 QALY (sunitinib vs BSC)	Discounted: AR$52,243 (sunitinib vs BSC)	AR$53,445 per QALY (sunitinib vs BSC)
Casciano et al (127)	2011	USA	To examine the potential cost-effectiveness of everolimus vs sorafenib therapy for the treatment of metastatic renal cell carcinoma after failure of first-line sunitinib from a US payer perspective	Patients with metastatic RCC after failure of first-line sunitinib.	Markov model. Time horizon of 6 years with 8-week cycles. Four health states: SD no AEs, SD with AEs, PD, death. Transition probabilities based on analysis of patient-level data from RCT and single-arm trial, utilities from the PenTAG (UK analysis) report.	Discounted: 0.916 QALY (everolimus vs sorafenib)	Discounted: $81,643 (everolimus vs sorafenib)	$89,160 per QALY (everolimus vs sorafenib)

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Contreras-Hernandez et al (115)	2007	Mexico	To compare the economic and health consequences of sunitinib vs BSC in adult patients with mRCC who failed prior cytokine treatment from a health care payer's perspective in Mexico	Adult patients failing cytokine therapies with metastatic RCC in stages III and IV.	Markov model. Time horizon of ten years. Four health states: no new progression, death due to metastatic RCC, history of new progression, death due to other causes. Transition probabilities and QALYs obtained according to clinical trials from the published literature.	Discounted: sunitinib: 1.32 QALYs; BSC: 0.39 QALYs	Discounted: sunitinib: US$36,928; BSC: US$4,103	US$35,238 per QALY (sunitinib vs BSC)
El Ouagari et al (116)	2010	Canada†	To compare the cost-effectiveness of everolimus vs BSC in patients who failed on VEGF-TKI therapy from a Canadian societal perspective	Metastatic RCC patients whose disease failed on VEGF-TKI therapies.	Markov model simulating 2 hypothetical patient cohorts, using a 6 year time horizon. Health state transition probabilities were derived from a RCT and costs and utilities were drawn from literature.	Discounted: 0.469 QALY (everolimus vs BSC)	Discounted: $29,080 (everolimus vs BSC)	$62,067 per QALY (everolimus vs BSC)

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Gao et al (117)	2006	USA	To evaluate the cost –effectiveness of sorafenib + BSC versus BSC alone in advanced RCC from a UK payer perspective	Patients with advanced RCC‡.	Markov model to project lifetime survival. Three health states: PFS, progression, death. Transition probabilities were obtained from a RCT.	Not reported	Lifetime per patient, discounted: sorafenib + BSC: $85,571; BSC: $36,634	Not reported $75,354 per LYG (sorafenib + BSC vs BSC)
Gao et al§ (118)	2008	USA	To update the earlier economic model (reported in (117) with the latest clinical data to evaluate the cost-effectiveness of sorafenib + BSC versus BSC alone in advanced RCC from a US payer perspective	Patients with advanced RCC‡.	Markov model to project lifetime survival. Three health states: PFS, progression, death. Transition probabilities were obtained from a RCT.	Not reported 0.88 discounted life years (sorafenib + BSC vs BSC)	Lifetime per patient, discounted: sorafenib + BSC: $92,222; BSC: $36,634	Not reported $63,219 per LYG (sorafenib + BSC vs BSC)
Hoyle et al (119)	2010	UK	To estimate the cost-effectiveness of sorafenib vs BSC for the second-line treatment of advanced renal cell carcinoma from the perspective of the UK NHS	Patients with advanced RCC, resistant to standard therapy; 82% had previously received cytokine-based therapy.	Markov model with a 10-year time horizon and 6-week cycles. Three health states: PFS, PD, death. Utilities were derived from a phase II single-arm trial of sunitinib. Clinical effectiveness from a RCT of sorafenib vs placebo.	Discounted: 0.27 QALY (sorafenib vs BSC)	Discounted: £20,063 (sorafenib vs BSC)	£75,398 per QALY (sorafenib vs BSC)

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Jaszewski et al (120)	2007	Canada	To evaluate the cost-effectiveness of sorafenib + BSC vs BSC alone in advanced RCC from a Canadian provincial Ministry of Health perspective	Patients with advanced RCC‡.	Markov model to project lifetime survival. Three health states: PFS, progression, death.	Not reported	Lifetime per patient, discounted: sorafenib + BSC: CAD$62,426; BSC: CAD$18,898	Not reported CAD$36,046 per LYG (sorafenib + BSC vs BSC)
Ondrackova et al¶ (128)	2010	Czech Republic	To assess the cost-effectiveness of sorafenib and sunitinib for the treatment of mRCC in reimbursement proceedings vs data from clinical practice	Patients with advanced or metastatic RCC after cytokine intolerance or failure.	Not reported The study compared cost-effectiveness results from manufacturers' submissions with own analysis results based on patient data from comprehensive cancer centre clinical practice (comparator: 70% treated with sunitinib and 30% treated with BSC).	Not reported	Not reported	Not reported Manufacturer submission: €37,143 per progression-free year (sorafenib vs sunitinib or BSC) New analysis: €19,878 per progression-free year (sorafenib vs sunitinib or BSC)

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Paz-Ares et al (121)	2010	Spain	To investigate the cost-effectiveness of sunitinib vs BSC in patients with cytokine refractory mRCC from the perspective of the Spanish NHS	Patients with metastatic RCC who did not respond to, were intolerant to or experienced disease progression on IL-2 or IFN-alpha. The model included characteristics of a Spanish population: average age of 62 years and 66% men and 34% women.	Markov model with a 10-year time horizon and a 4-week cycle length. Three health states: PFS, survival with progression, death from metastatic RCC or other causes. Utilities and effectiveness data were obtained from a phase II study of sunitinib-treated patients.	Discounted: sunitinib: 1.36 QALYs; BSC: 0.39 QALYs	Discounted: €32,911 (sunitinib vs BSC)	€34,196 per QALY (sunitinib vs BSC)

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Pitt et al[††] (122)	2010	UK	ERG report on the manufacturer's submission: Single Technology Appraisal for everolimus (Afinitor®) in advanced renal cell carcinoma	Heavily pre-treated adult (≥18 years) advanced RCC patients who have experienced disease progression on or following one or more VEGF-targeted therapies (sunitinib, sorafenib and/or bevacizumab).	Markov model with 8-week cycles and a 144 week-time horizon. Four health states: stable disease with AEs, stable disease without AEs, progressed, death. Utility data from the PenTAG report was used and effectiveness data was obtained from a RCT.	Manufacturer submission: With patient-access scheme, discounted: 0.304 QALY (everolimus + BSC vs BSC) ERG re-analysis: With patient-access scheme, discounted: 0.193 QALY (everolimus + BSC vs BSC)	Manufacturer submission: With patient-access scheme, discounted: £15,704 (everolimus + BSC vs BSC) ERG re-analysis: With patient-access scheme, discounted: £12,610 (everolimus + BSC vs BSC)	Manufacturer submission: With PAS: £51,613 per QALY (everolimus + BSC vs BSC) ERG re-analysis: With PAS: £65,231 per QALY (everolimus + BSC vs BSC)

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Purmonen et al (123)	2008	Finland	To analyse the cost-effectiveness of sunitinib as second-line therapy for cytokine-refractory mRCC compared with BSC in Finland	Patients with metastatic RCC (median age 68 years), previously treated with IFN-α (69% male, 31% female).	Markov model with 5-year time horizon and 1-month cycles. Three health states: no new progression events, history of progression-related events, death. Transition probabilities and utilities were obtained from a phase II single-arm trial and a beta distribution was used for uncertainty regarding BSC utilities.	Discounted: 0.74 QALY (sunitinib vs BSC)	Discounted, per patient, for 5 years: €32,630 (sunitinib vs BSC)	€43,698 per QALY (sunitinib vs BSC)
Tatar et al (124)	2009	Turkey	To assess the cost-effectiveness of sorafenib + BSC versus BSC alone in mRCC patients in Turkey	Patients with unresectable and/or metastatic RCC‡.	Markov model over a patient's lifetime. Three health states: PFS, disease progression, death. PFS and survival were extrapolated from a RCT.	Not reported 1.269 discounted LYG (sorafenib + BSC vs BSC)	Lifetime per patient, discounted: sorafenib + BSC: 47,665 TL; BSC: 4,080 TL	Not reported 34,342 TL per LYG (sorafenib + BSC vs BSC)

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Teich et al (125)	2009	Brazil	To develop a cost-effectiveness analysis of sorafenib + BSC vs BSC alone in the second-line treatment of advanced RCC from the Brazilian public health care system perspective	Advanced RCC (second-line treatment).	Markov model with a lifetime time horizon and a 3-month cycle. Three health states: PFS, disease progression, death. Transition probabilities were obtained from a RCT.	Not reported Mean PFS: 2066 years (sorafenib/BSC); 1243 years (BSC)	Lifetime, discounted: sorafenib/BSC: R$48,285; BSC: R$7,356	Not reported R$49,751 (US$21,553) per LYG (sorafenib/BSC vs BSC)
Thompson-Coon et al[§§] (126)	2010	UK	To assess the cost-effectiveness of bevacizumab, combined with IFN, sorafenib tosylate, sunitinib and temsirolimus in the treatment of advanced/mRCC	All patients in the model were assumed to have advanced/metastatic RCC and all patients were assumed to start in PFS.	Markov model with 10-year time horizon and 6-week cycles. Three health states: progression-free, progressive, death. Weibull curves were fitted to empirical effectiveness data from a RCT. Utility data was obtained from manufacturer submissions.	Discounted: 0.23 QALY (sorafenib vs BSC)	Discounted: £24,001 QALY (sorafenib vs BSC)	£102,498 per QALY (sorafenib vs BSC)

Study	Year	Country where study was performed	Aim	Patient population (average age in years)	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Van Nooten et al (129)	2007	Belgium	To determine the cost-effectiveness of sunitinib malate vs BSC after failure of cytokine immunotherapy from the perspective of the Belgian public payers	Patients with metastatic RCC after failure on first-line cytokine therapy.	Markov model with a 10-year time horizon and a one-month cycle length. Three health states: PFS, tumour progression and move to BSC, death. Effectiveness parameters for sunitinib were taken from a phase II clinical trial. Utilities were derived from published literature.	Not reported Average discounted 1.11 LYG per patient (sunitinib vs BSC)	Not reported	Not reported €35,389 per LYG (sunitinib vs BSC)

Abbreviations: AE, adverse event; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IFN, interferon; IL, interleukin; LYG, life-year gained; mRCC, metastatic renal cell carcinoma; NHS, National Health Service; PAS, patient access scheme; PenTAG, Peninsula Technology Assessment Group; PD, progressive disease; PFS, progression-free survival; QALY(s), quality-adjusted life year(s); RCC, renal cell carcinoma; RCT, randomised controlled trial; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

[†]It is not clear from this abstract if the costs are in US$ or CA$.
[‡]It is not clear from the abstract if the patients are second-line treated, but it was assumed that the patients were second-line RCC patients, because data was used from the (second-line) TARGET trial.
[§]This analysis updated the Gao et al 2006 analysis, using latest overall survival data.
[¶]This abstract describes two cost-effectiveness analyses: first-line sunitinib vs interferon-alpha and second-line sorafenib vs sunitinib or BSC. Only the second-line data is included in the systematic review.
[††]This ERG report was identified in the electronic database searches and the relevant manufacturer submission to NICE for everolimus was consulted for additional information.
[§§]This HTA document reports various comparisons, however only the second-line treatment comparison (sorafenib vs BSC) is included in the systematic review. The manufacturer submissions and the ERG report (PenTAG report) were also consulted for additional information

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

Only full publications were quality assessed.

Casciano et al 2011 (127)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	NA
2. Was the economic importance of the research question stated?	Not clear	The burden of mRCC is described; it is implied that the economic evaluation of the studied comparison is imperative following a recent indirect comparison
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	US payer perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Improved OS outcomes with everolimus in an indirect comparison with sorafenib in sunitinib-refractory patients
5. Were the alternatives being compared clearly described?	Yes	NA
6. Was the form of economic evaluation stated?	Not clear	The text implies a CEA and CUA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	The form of economic evaluation is not stated, but the question can be answered with the analyses
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	NA
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Not clear	For transition probabilities, data from a RCT and non-RCT were used; none were described in detail.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	NA
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	NA
12. Were the methods used to value health states and other benefits stated?	Not clear	For health utilities, the PenTAG report was used, one decrement was included for one AE; not described in detail

Casciano et al 2011 (127)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Only that they were second-line patients unsuitable for interferon
14. Were productivity changes (if included) reported separately?	No	Payer perspective adopted; no productivity changes included
15. Was the relevance of productivity changes to the study question discussed?	No	NA
16. Were quantities of resources reported separately from their unit cost?	Yes	Unit costs and cost per 8-week cycle
17. Were the methods for the estimation of quantities and unit costs described?	Not clear	Methods for estimation of unit costs were described (using a weighted average), but not described why an 8-week cycle length was chosen
18. Were currency and price data recorded?	Yes	NA
19. Were details of price adjustments for inflation or currency conversion given?	No	NA
20. Were details of any model used given?	Yes	NA
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Model and key parameters are presented, however justification was not detailed
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	6 years
23. Was the discount rate stated?	Yes	3.0% annually (costs and effects)
24. Was the choice of rate justified?	No	NA
25. Was an explanation given if cost or benefits were not discounted?	NA	NA
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	NA
27. Was the approach to sensitivity analysis described?	Yes	NA
28. Was the choice of variables for sensitivity analysis justified?	No	NA
29. Were the ranges over which the parameters were varied stated?	Yes	NA

Casciano et al 2011 (127)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	NA
31. Was an incremental analysis reported?	Yes	NA
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	NA
33. Was the answer to the study question given?	Yes	The ICER is presented for the comparison of everolimus vs sorafenib and is considered cost-effective for a WTP threshold of $100,000/QALY
34. Did conclusions follow from the data reported?	Yes	NA
35. Were conclusions accompanied by the appropriate caveats?	Yes	Regarding time horizon of survival; AE rates and costs; generalisability of the patient population; and limitation of data sources
36. Were generalisability issues addressed?	Yes	NA

Hoyle et al 2010 (119)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	NA
2. Was the economic importance of the research question stated?	Yes	As part of the independent assessment report submitted to NICE
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS and PSS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	A cost-effectiveness analysis was used in the manufacturer submission for this comparison
5. Were the alternatives being compared clearly described?	Not clear	The definition of BSC is not described clearly
6. Was the form of economic evaluation stated?	Not clear	The text implies a CEA and CUA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	The form of economic evaluation is not stated, but the question can be answered with the analyses

Hoyle et al 2010 (119)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	A RCT
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	NA
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	NA
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	NA
12. Were the methods used to value health states and other benefits stated?	Yes	Derived from a phase II single-arm trial of sunitinib, from UK EQ-5D tariffs
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Only that patients were on second-line treatment
14. Were productivity changes (if included) reported separately?	No	NA
15. Was the relevance of productivity changes to the study question discussed?	No	NA
16. Were quantities of resources reported separately from their unit cost?	Yes	Unit costs and cost per 6-week cycle
17. Were the methods for the estimation of quantities and unit costs described?	Yes	NA
18. Were currency and price data recorded?	Yes	NA
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Inflated to 2007/2008 values using the Hospital & Community Health Services Pay and Prices Index
20. Were details of any model used given?	Yes	NA
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The model and key parameters are presented and justified
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	10 years

Hoyle et al 2010 (119)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
23. Was the discount rate stated?	Yes	3.5% per year (costs and benefits)
24. Was the choice of rate justified?	Yes	Not explicitly, but a reference to NICE guidelines is included
25. Was an explanation given if cost or benefits were not discounted?	NA	NA
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Weibull curves were used and explained for survival analyses
27. Was the approach to sensitivity analysis described?	Yes	NA
28. Was the choice of variables for sensitivity analysis justified?	No	NA
29. Were the ranges over which the parameters were varied stated?	Yes	NA
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	NA
31. Was an incremental analysis reported?	Yes	NA
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	NA
33. Was the answer to the study question given?	Yes	With an incremental >£70,000/QALY compared to BSC, sorafenib may not be regarded as a cost-effective use of resources in some health-care settings
34. Did conclusions follow from the data reported?	Yes	NA
35. Were conclusions accompanied by the appropriate caveats?	Yes	Regarding the scarcity of available data; generalisability of the patient population; disutility estimate due to hypertension; and dose intensity estimates
36. Were generalisability issues addressed?	Yes	Regarding the population (clear-cell RCC and prior nephrectomy) and possible difference between RCT and normal clinical practice

Paz-Ares et al 2010 (121)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	NA
2. Was the economic importance of the research question stated?	Not clear	The burden of RCC is described, but the study does not clarify the economic importance of the cost-effectiveness evaluation of sunitinib vs BSC
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Spanish National Health Service
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Only a small proportion of patients benefits from cytokines and sunitinib has shown benefit in this population as alternative to BSC
5. Were the alternatives being compared clearly described?	Yes	NA
6. Was the form of economic evaluation stated?	Not clear	The text implies a CEA and CUA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	The form of economic evaluation is not stated, but the question can be answered with the analyses
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	A single-arm phase II study and a database for effects of BSC
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	NA
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	NA
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	NA
12. Were the methods used to value health states and other benefits stated?	Yes	NA
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Not explicitly stated, but a reference is included
14. Were productivity changes (if included) reported separately?	No	NA

Paz-Ares et al 2010 (121)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
15. Was the relevance of productivity changes to the study question discussed?	No	NA
16. Were quantities of resources reported separately from their unit cost?	Yes	Unit costs are presented and quantities per treatment, but costs per cycle per treatment comparator are not presented
17. Were the methods for the estimation of quantities and unit costs described?	Yes	NA
18. Were currency and price data recorded?	Yes	NA
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Costs were updated to reflect the 2007 rate in euros by applying the corresponding CPI rates
20. Were details of any model used given?	Yes	NA
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	No justification of the model is given, although the model and key parameters are described and clarified
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	10 years
23. Was the discount rate stated?	Yes	3.5% annual discount for both costs and effects
24. Was the choice of rate justified?	Yes	NICE recommendation
25. Was an explanation given if cost or benefits were not discounted?	NA	NA
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	Only reported that survival data was taken from a single-arm phase II trial
27. Was the approach to sensitivity analysis described?	Yes	NA
28. Was the choice of variables for sensitivity analysis justified?	No	NA
29. Were the ranges over which the parameters were varied stated?	No	NA
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	NA
31. Was an incremental analysis reported?	Yes	NA

Paz-Ares et al 2010 (121)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	NA
33. Was the answer to the study question given?	Not clear	It is stated that Spain has no clear WTP threshold, but a rate between €30,000/QALY and €50,000/QALY; cost-effectiveness of sunitinib vs BSC was estimated at €34,196/QALY and cost-effectiveness remains therefore uncertain
34. Did conclusions follow from the data reported?	Not clear	It is concluded that "sunitinib has a good cost-effectiveness profile in mRCC" (€34,196/QALY vs BSC)
35. Were conclusions accompanied by the appropriate caveats?	Yes	Regarding sources of data; comparator (e.g. cytokine rather than BSC); and perspective of analysis (societal, rather than payer)
36. Were generalisability issues addressed?	Yes	It is stated that data from the trials may not reflect daily practice

Purmonen et al 2008 (123)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	NA
2. Was the economic importance of the research question stated?	No	NA
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The health care payer in Finland
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	NA
5. Were the alternatives being compared clearly described?	Not clear	There is a reference to clinical trials and BSC is defined as palliative biochemotherapy
6. Was the form of economic evaluation stated?	Not clear	The text implies a CEA and CUA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	The form of economic evaluation is not stated, but the question can be answered with the analyses

Purmonen et al 2008 (123)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	From clinical trials for sunitinib and patient-level data for BSC
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Not clear	Not explicitly, but there is a reference to the publication of the study
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	NA
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	NA
12. Were the methods used to value health states and other benefits stated?	Yes	Utilities were taken from the sunitinib trial
13. Were the details of the subjects from whom valuations were obtained given?	Yes	NA
14. Were productivity changes (if included) reported separately?	No	The payer perspective has been used, indirect costs were not assessed
15. Was the relevance of productivity changes to the study question discussed?	No	NA
16. Were quantities of resources reported separately from their unit cost?	No	NA
17. Were the methods for the estimation of quantities and unit costs described?	Yes	The recommended unit costs for health care services were case-mix adjusted for Finnish regional price differences and real-valued to 2005 using the official health care price index.
18. Were currency and price data recorded?	Yes	NA
19. Were details of price adjustments for inflation or currency conversion given?	Yes	“Prices from previous years were not converted to 2005 currency because medications in Finland do not follow the general price index, partly because wholesale prices for medications in Finland were cut by 5% in 2006 and also due to the launch of the generic substitution program in 2003.”

Purmonen et al 2008 (123)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
20. Were details of any model used given?	Yes	NA
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	NA
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	5 years
23. Was the discount rate stated?	Yes	Both costs and QALYs at 5% annually
24. Was the choice of rate justified?	No	NA
25. Was an explanation given if cost or benefits were not discounted?	NA	NA
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	NA
27. Was the approach to sensitivity analysis described?	Yes	NA
28. Was the choice of variables for sensitivity analysis justified?	Not clear	Not for the discount rates and time horizon, but it is explained for the different age groups
29. Were the ranges over which the parameters were varied stated?	Not clear	Only the different age range was given, but not the different other parameters
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	NA
31. Was an incremental analysis reported?	Yes	NA
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	NA
33. Was the answer to the study question given?	Not clear	The ICER is given, but the Finnish WTP threshold is not clearly explained
34. Did conclusions follow from the data reported?	Yes	NA
35. Were conclusions accompanied by the appropriate caveats?	Yes	Regarding patient data; survival time estimates; and generalisability of clinical practice vs trial setting

Purmonen et al 2008 (123)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
36. Were generalisability issues addressed?	Yes	Regarding the differences in patient populations and treatments between the clinical trial and in clinical practice in Finland

Thompson-Coon et al 2010 HTA(126)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	NA
2. Was the economic importance of the research question stated?	Yes	NA
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS and PSS in UK
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	NA
5. Were the alternatives being compared clearly described?	No clear	The interventions were not described in detail
6. Was the form of economic evaluation stated?	Yes	NA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	NA
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Data from a RCT and Weibull curves of the data from the RCT for BSC
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Not clear	Not much data is presented, but a reference is given
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	NA
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	NA
12. Were the methods used to value health states and other benefits stated?	Not clear	It is described that starting values for first-line and second-line patients are similar

Thompson-Coon et al 2010 HTA(126)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	It is referred to the Pfizer submission for sunitinib
14. Were productivity changes (if included) reported separately?	No	The NHS and PSS perspective was used
15. Was the relevance of productivity changes to the study question discussed?	No	NA
16. Were quantities of resources reported separately from their unit cost?	Yes	NA
17. Were the methods for the estimation of quantities and unit costs described?	Yes	NA
18. Were currency and price data recorded?	Yes	NA
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Pounds Sterling, inflated to 2007-08
20. Were details of any model used given?	Yes	NA
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	NA
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	10 years
23. Was the discount rate stated?	Yes	Future costs and benefits at 3.5% per annum
24. Was the choice of rate justified?	Yes	Not explicitly, but a reference to NICE guidelines is included
25. Was an explanation given if cost or benefits were not discounted?	NA	NA
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	For the Weibull curves
27. Was the approach to sensitivity analysis described?	Yes	NA
28. Was the choice of variables for sensitivity analysis justified?	Yes	NA
29. Were the ranges over which the parameters were varied stated?	Yes	NA

Thompson-Coon et al 2010 HTA(126)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	NA
31. Was an incremental analysis reported?	Yes	NA
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	NA
33. Was the answer to the study question given?	Yes	Only at a WTP threshold of £100,000/QALY
34. Did conclusions follow from the data reported?	Yes	NA
35. Were conclusions accompanied by the appropriate caveats?	Yes	Regarding clinical trial methods and cross-over; prices; utility sources; and generalisability
36. Were generalisability issues addressed?	Yes	Regarding patient populations from trials

Pitt et al 2010 (ERG report and Novartis submission) (122)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	Not explicitly, but it is clear from the text that this ERG investigates the methods for cost-effectiveness analysis as conducted by Novartis for the purpose of the NICE STA submission
2. Was the economic importance of the research question stated?	Yes	Not explicitly, but it is clear from the context (ERG report)
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS and PSS in the UK
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	NA
5. Were the alternatives being compared clearly described?	Yes	NA
6. Was the form of economic evaluation stated?	Yes	NA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	NA

Pitt et al 2010 (ERG report and Novartis submission) (122)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	RCT
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	In different sections (clinical effectiveness)
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	NA
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	NA
12. Were the methods used to value health states and other benefits stated?	Yes	PenTAG report and AEs from Doyle et al 2008
13. Were the details of the subjects from whom valuations were obtained given?	No	NA
14. Were productivity changes (if included) reported separately?	No	The NHS and PSS perspective was used
15. Was the relevance of productivity changes to the study question discussed?	No	NA
16. Were quantities of resources reported separately from their unit cost?	Yes	NA
17. Were the methods for the estimation of quantities and unit costs described?	Yes	NA
18. Were currency and price data recorded?	Yes	NA
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Pounds Sterling inflated to 2008
20. Were details of any model used given?	Yes	NA
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	NA
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	144 weeks
23. Was the discount rate stated?	Yes	3.5% per annum for costs and benefits

Pitt et al 2010 (ERG report and Novartis submission) (122)		
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
24. Was the choice of rate justified?	Yes	NICE reference case
25. Was an explanation given if cost or benefits were not discounted?	NA	NA
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	NA
27. Was the approach to sensitivity analysis described?	Yes	NA
28. Was the choice of variables for sensitivity analysis justified?	Yes	NA
29. Were the ranges over which the parameters were varied stated?	Yes	NA
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	NA
31. Was an incremental analysis reported?	Yes	NA
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	NA
33. Was the answer to the study question given?	Yes	NA
34. Did conclusions follow from the data reported?	Yes	NA
35. Were conclusions accompanied by the appropriate caveats?	Yes	Regarding trial design; used utility values; and resource utility data
36. Were generalisability issues addressed?	Not clear	Only that the trial population may not be the same as in actual clinical practice

10.12 Appendix 12: Search strategy for Section 7.4 (Measurement and valuation of health effects)

10.12.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***NHS EED***
- ***EconLIT***

The following databases were searched:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- Embase 1974 to 2012 June 08
- EconLIT 1961 to May 2012
- Cochrane Library: Health Technology Assessment 2nd Quarter 2012, NHS Economic Evaluation Database 2nd Quarter 2012

10.12.2 *The date on which the search was conducted.*

All searches were conducted on 11th June 2012.

10.12.3 *The date span of the search.*

All searches were conducted from 2006 - 11th June 2012.

Because the PenTAG report did not identify any relevant publications published prior to 2006, this year was chosen as cut-off year.

10.12.4 *The complete search strategies used, including all the search terms textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

Embase 1974 to 2012 June 08, searched 11-06-2012

	Searches	Results
1	exp kidney metastasis/ or kidney metastas$.ab,ti.	1519
2	exp kidney carcinoma/ or (metastatic renal cell carcinoma or mrcc).ab,ti.	38637
3	renal cell neoplasm.ab,ti.	16
4	renal carcinoma.ab,ti.	4418
5	(renal cell cancer or renal cancer$).ab,ti.	6540

6	renal cell carcinoma.ab,ti.	24660
7	exp metastasis/ or metastas$.ab,ti.	405529
8	exp kidney/ or (renal or kidney).ab,ti.	832379
9	7 and 8	23507
10	1 or 2 or 3 or 4 or 5 or 6 or 9	56091
11	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	19814
12	(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3103
13	(Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4419
14	(Health utilities index or HUI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1986
15	(time trade off or TTO).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1134
16	(standard gamble or SG).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	6771
17	quality of life.mp. or *"quality of life"/	243208
18	health status.mp. or *health status/	89123
19	health status indicators.mp.	581
20	activities of daily living.mp. or *daily life activity/	23289
21	*health survey/ or health survey*.mp.	145142

22	quality adjusted life years.mp. or *quality adjusted life year/	4256
23	psychometrics.mp. or *psychometry/	8901
24	(QOL or HRQOL or HRQL or QALY*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	38774
25	(health* year* equivalent* or HYE*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1003
26	(Quality of wellbeing index or QWB).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	175
27	(medical outcomes survey or MOS).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	6644
28	(willingness to pay or WTP).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2764
29	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 or 26 or 27 or 28	487194
30	10 and 29	1484
31	limit 30 to (english and yr="2006 -Current")	915

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, searched 11-06-2012

	Searches	**Results**
1	kidney metastas$.ab,ti.	60
2	exp Carcinoma, Renal Cell/ or (metastatic renal cell carcinoma or mrcc).ab,ti.	20124
3	renal cell neoplasm.ab,ti.	12

4	renal carcinoma.ab,ti.	3557
5	(renal cell cancer or renal cancer$).ab,ti.	4980
6	renal cell carcinoma.ab,ti.	18611
7	exp Neoplasm Metastasis/ or metastas$.ab,ti.	274537
8	exp kidney/ or (renal or kidney).ab,ti.	669540
9	7 and 8	14647
10	1 or 2 or 3 or 4 or 5 or 6 or 9	35571
11	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	13181
12	(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2070
13	(Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2888
14	(Health utilities index or HUI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	888
15	(time trade off or TTO).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	868
16	(standard gamble or SG).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	5218
17	quality of life.mp. or *"Quality of Life"/	159633
18	health status.mp. or *Health Status/	90706
19	health status indicators.mp. or *Health Status Indicators/	18049

20	*"Activities of Daily Living"/	12934
21	*Health Surveys/ or health survey*.mp.	54262
22	*Quality-Adjusted Life Years/	1234
23	quality adjusted life year*.mp.	7791
24	*Psychometrics/ or psychometric*.mp.	57352
25	(QOL or HRQOL or HRQL or QALY).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	25063
26	(health* year* equivalent* or HYE*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	631
27	(Quality of wellbeing index or QWB).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	153
28	(medical outcomes survey or MOS).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	4610
29	(willingness to pay or WTP).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1944
30	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 or 26 or 27 or 28 or 29	343618
31	10 and 30	574
32	limit 31 to (yr="2006 -Current" and english)	270

QoL, Cochrane Library: Health Technology Assessment 2nd Quarter 2012, **NHS Economic Evaluation Database** 2nd Quarter 2012, searched on 11-06-2012

	Searches	**Results**
1	kidney metastas$.ab,ti.	0

2	exp Carcinoma, Renal Cell/ or (metastatic renal cell carcinoma or mrcc).ab,ti.	54
3	renal cell neoplasm.ab,ti.	0
4	renal carcinoma.ab,ti.	1
5	(renal cell cancer or renal cancer$).ab,ti.	10
6	renal cell carcinoma.ab,ti.	45
7	exp Neoplasm Metastasis/ or metastas$.ab,ti.	229
8	exp kidney/ or (renal or kidney).ab,ti.	380
9	7 and 8	11
10	1 or 2 or 3 or 4 or 5 or 6 or 9	65
11	(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp. [mp=ti, tx, hw]	240
12	(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp. [mp=ti, tx, hw]	33
13	(Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp. [mp=ti, tx, hw]	566
14	(Health utilities index or HUI).mp. [mp=ti, tx, hw]	89
15	(time trade off or TTO).mp. [mp=ti, tx, hw]	322
16	(standard gamble or SG).mp. [mp=ti, tx, hw]	190
17	quality of life.mp. or *"Quality of Life"/	5274
18	health status.mp. or *Health Status/	512
19	health status indicators.mp. or *Health Status Indicators/	50
20	*"Activities of Daily Living"/	0
21	*Health Surveys/ or health survey*.mp.	162
22	*Quality-Adjusted Life Years/	0
23	quality adjusted life year*.mp.	3389
24	*Psychometrics/ or psychometric*.mp.	42
25	(QOL or HRQOL or HRQL or QALY).mp. [mp=ti, tx, hw]	2431

26	(health* year* equivalent* or HYE*).mp. [mp=ti, tx, hw]	6
27	(Quality of wellbeing index or QWB).mp. [mp=ti, tx, hw]	14
28	(medical outcomes survey or MOS).mp. [mp=ti, tx, hw]	11
29	(willingness to pay or WTP).mp. [mp=ti, tx, hw]	643
30	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 or 26 or 27 or 28 or 29	5817
31	10 and 30	19
32	limit 31 to (english language and yr="2006 -Current")	14

Econlit 1961 to May 2012, searched 11-06-2012

	Searches	Results
1	kidney metastas$.ab,ti.	0
2	(metastatic renal cell carcinoma or mrcc).ab,ti.	0
3	renal cell neoplasm.ab,ti.	0
4	renal carcinoma.ab,ti.	0
5	(renal cell cancer or renal cancer$).ab,ti.	0
6	renal cell carcinoma.ab,ti.	2
7	metastas$.ab,ti.	8
8	(renal or kidney).ab,ti.	147
9	7 and 8	1
10	1 or 2 or 3 or 4 or 5 or 6 or 9	2

10.12.5 *Details of any additional searches, such as searches of company databases (include a description of each database).*

The following conferences were searched (for 2011-2012):

- American Society of Clinical Oncology (ASCO), including Genitourinary Symposium and Annual Meeting.

- European Cancer Organisation (ECCO) and European Society for Medical Oncology (ESMO).
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR), including Annual International Meeting, European Meeting and other meetings.

In addition, the following sources were searched:

- Cost Effectiveness Analysis Registry, using the search terms “renal cell carcinoma” and “RCC”.
- EQ-5D websitef, using the search terms “renal cell carcinoma” and “RCC”.
- Research Papers in Economics (RePEc) websiteg, using the search terms “renal cell carcinoma” and “RCC”.
- The NICE website for evidence review group reports, manufacturer submissions and other relevant documents for second-line RCC treatments.
- Reference lists of included publications and relevant reviews.

10.12.6 *The inclusion and exclusion criteria.*

Criteria	Include	Exclude
Population	Adults with advanced or metastatic RCC	Paediatric populations and other indications
Intervention	No restriction	NA
Comparator	No restriction	NA
Outcomes	HRQoL outcomes: EQ-5D utilities. Utilities derived from generic preference-based instruments such as the SF-36, SF-12, SF-6D, HUI2 or HUI3. Utilities derived using mapping algorithms. Mapping algorithms.	NA
Setting	Any	Not limited
Study design	Not restricted	Case studies, reviews or editorials, utilities based on expert opinion
Language of publication	English (English abstracts of non-English publications will be included)	Non-English publications
Date of publication	2006 onwards	Publications published prior to

[f] www.euroqol.org

[g] http://repec.org/docs/RePEcIntro.html

	2011 onwards for conference abstracts	2006

10.12.7 *The data abstraction strategy.*

Data was extracted into the summary tables by a reviewer. Uncertainties were resolved following discussion with a second reviewer.

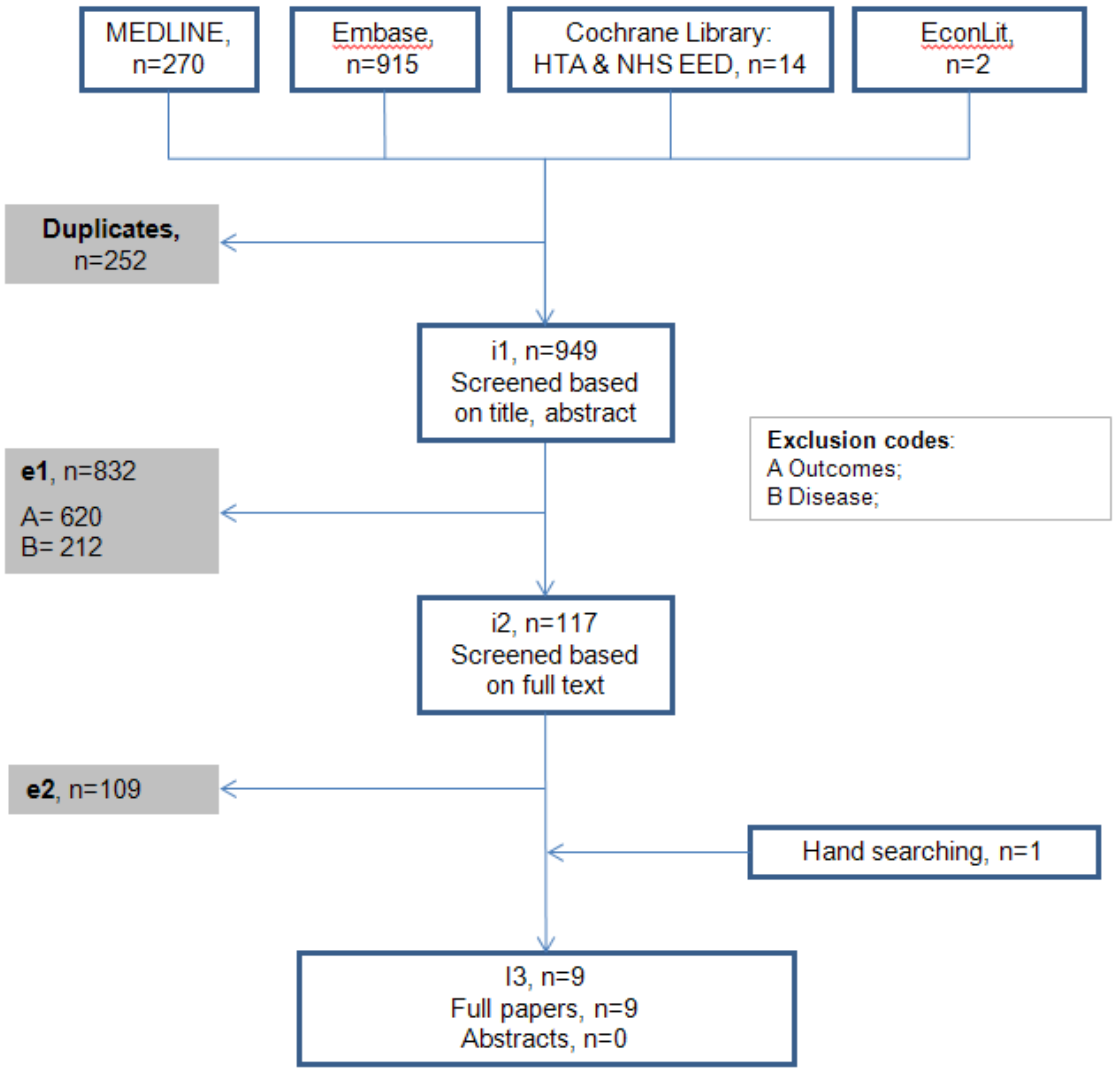
10.12.8 *Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used.*

A systematic review was conducted to identify HRQoL studies from the published literature that reported health state utility values (in particular EQ-5D) relating to advanced/mRCC. The following electronic databases were searched; MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), Embase, EconLIT, Cochrane Library: Health Technology Assessment 2nd Quarter 2012, NHS Economic Evaluation Database 2nd Quarter 2012. Electronic searches were supplemented by hand searching the following sources; conference proceedings, relevant NICE submission/appraisal data, CEA Registry, the EQ-5D website and the Research Papers in Economics (RePEc) website.

Full details of the databases, conference proceedings, search strategies employed and inclusion/exclusion criteria are presented in Appendix 12 (Section 10.12)

In total, 1,201 papers were identified through the electronic searches. Upon removal of duplicates, 949 titles and abstracts were reviewed. Of these, 117 full publications were reviewed, of which 109 were excluded, resulting in 8 publications for final inclusion. One further study was identified by hand searching (Figure 43).

Figure 43: Flow diagram for the systematic review of HRQoL data



10.12.9 *Provide details of the studies in which HRQL is measured.*

Details of the studies identified in the systematic review are presented in Table 68.

Table 68: Summary list of HRQoL studies

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility score
Castellano 2009 (136)	France, Germany, Italy, Poland, Spain and the UK	European patients aged >18 with mRCC who had not previously been treated with systemic therapy	Sunitinib 50mg/d/4 weeks (oral capsule) followed by two weeks of treatment in repeated 6-week cycles of treatment. INF-α was administered as an SC injection in 6-week cycles on three non-consecutive days of the week. Subjects received 3 MU/dose in the first week, 6 MU/dose in the second week, and 9 MU/dose thereafter	304 patients were recruited at random	EQ-5D	Baseline-sunitinib malate (mean)	0.72 (SD 0.24)
						Baseline-IFN-α (mean)	0.74 (SD 0.25)
						Sunitinib- over the first 6-cycles (LSM)	0.723
						INF- α- over the first 6-cycles (LSM)	0.674
Cella 2011 (49)	Global	Patients aged 18 years or over, either treatment-naïve or cytokine-pretreated, with locally advanced/mRCC (stage IV) of clear cell or predominantly	Pazopanib 800 mg per day or matching placebo	435 patients (data available from 398 patients)	EQ-5D (mean, SD)	Baseline	Placebo 0.73, 0.24
							Pazopanib 0.72, 0.25
						Week 6	Placebo 0.72, 0.30
							Pazopanib 0.71, 0.22
						Week 12	Placebo 0.75, 0.23
							Pazopanib 0.70, 0.25
						Week 18	Placebo 0.76, 0.22
							Pazopanib 0.71, 0.26

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility score
		clear cell histology and ECOG PS or 0 or 1				Week 24	Placebo 0.76, 0.23
							Pazopanib 0.71, 0.24
						Weed 48	Placebo 0.80, 0.24
							Pazopanib 0.79, 0.20
					Change from baseline (mean EQ-5D, SD)	Baseline	-
							-
						Week 6	Placebo -0.03, 0.27
							Pazopanib -0.01, 0.22
						Week 12	Placebo 0.01, 0.20
							Pazopanib -0.04, 0.21
						Week 18	Placebo -0.01, 0.15
							Pazopanib -0.02, 0.23
						Week 24	Placebo -0.001, 0.24
							Pazopanib -0.03, 0.24
						Week 48	Placebo -0.01, 0.20
							Pazopanib 0.03, 0.20
Cella 2010 (137)	Global Data also reported	Patients aged 18 years or over, with mRCC with a component of	Oral sunitinib 50 mg per day in 6 week cycles (4 weeks on, 2 weeks off treatment) or SC IFN-α 9 million units 3 times	750 total US group = 347 EU group = 274	EQ-5D (mean across all available post-baseline	Total group	Sunitinib 0.75
							IFN-α 0.69

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility score
	separately for US and European (France, Germany, Italy, Poland, Spain, UK) subgroups	clear cell histology	weekly	(France 82, Germany 17, Italy 24, Poland 103, Spain 27, UK 21)	observations)	EU group	Sunitinib 0.72
							IFN-α 0.71
						US group	Sunitinib 0.77
							IFN--α 0.75
Cella, 2008 (138)	International, multicentre	Patients with no previous treatment with systemic RCC therapy, ECOG status of 0 or 1	Patients were randomly assigned at a ratio of one to one to receive either sunitinib (starting dose of 50mg orally/day, in a 6-week cycle consisting of 4 week on treatment followed by 2 weeks off treatment) or IFN-α (3 MU three times/week on non-consecutive days in the first week, 6 MU in second week, and 9 MU thereafter)	Sunitinib= 375; IFN-α= 375	Three questionnaires were completed at screening on days 1 and 28 of each cycle and at end of treatment: FACT-G (27-item); FKSI-DRS (9-item scale);FKSI-15; EQ-VAS/EQ-5D (100-item VAS);	Baseline: Sunitinib	0.76 (0.23)
						Baseline IFN-α	0.76 (0.23)
						Sunitinib	Least square mean: 0.762
						IFN-α	IFN-α 0.725
						Average difference: 0.0364 (95%CI: 0.0109 to 0.0620; p=0.0052)	

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility score
Escudier (139)	Multicentre	Patients with cytokine refractory mRCC	Sunitinib (37.5mg/d), either in the AM or PM. The dose was titrated up to 50mg/d or down to 25mg/d on an individual basis depending on tolerability	107 patients enrolled (52 in the AM group and 52 in the PM group provided baseline EQ-5D. Response rate at subsequent visits was >95%	EQ-5D	Baseline-Sunitinib AM (median)	0.8
						Baseline-Sunitinib PM (median)	0.8
						*There was no evidence of a change in EQ-5D from baseline through up to 29 cycles of treatment and no statistically significant differences between cohorts	
Swinburn, 2010 (140)	UK	UK members of the general public (TTO test developed with mRCC patients)	None	100 members of the general public from London, Birmingham, Oxford and Leamington Spa	TTO	Stable disease/no AE	0.795 (CI: 0.761-0.830)
						Progressive	0.355 (CI: 0.299 0.412)
						Stable/anaemia grade III	0.676 (CI: 0.630 0.722)
						Stable/diarrhoea grade I/II	0.690 (CI: 0.641 0.738)
						Stable/diarrhoea grade III	0.534 (CI: 0.482 0.586)
						Stable/fatigue I/II	0.751 (CI: 0.710 0.792)
						Stable/fatigue grade III	0.591 (CI: 0.543 0.639)

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility score
						Stable/PPE grade III	0.469 (CI: 0.414 0.524)
						Stable/mucositis grade I/II	0.726 (CI: 0.681 0.771)
						Stable/mucositis grade III	0.526 (CI: 0.476 0.575)
						Stable/nausea grade I/II	0.635 (CI: 0.587 0.683)
						Stable/nausea III	0.540 (CI: 0.486 0.593)
						Stable/hypertension grade III	0.642 (CI: 0.594 0.690)
Uemura, 2010 (141)	Japan	Japanese patients with RCC (25 treatment naïve and 26 cytokine-refractory)	Sunitinib at a starting dose of 50 mg orally, once daily, in the morning, without regard to meals, in repeated 6-week cycles according to schedule 4/2 (4 weeks on treatment followed by 2 weeks off).	51 patients (25 treatment naïve and 26 cytokine-refractory)	EQ-5D and EQ-VAS	Range of mean change for EQ-5D Index at each end point from baseline was from -0.1573 to 0.0375 in the first-line population and from -0.0974 to 0.0513 in the second-line population. Range of mean change for EQ-VAS at each end point from baseline was from -12.35 to 2.71 in the first-line population and from -11.82 to 4.17 in the second-line population.	

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility score
Yang, 2010 (142)	Global	Subgroup of 626 patients with previously untreated, poor-prognosis advanced RCC from Global ARCC	Patients were randomly assigned to 25 mg of intravenous temsirolimus weekly or 3–18mU of subcutaneous IFN-α 3 x weekly	Of these 416 patients, 270 (65%) were evaluable for QoL analysis	EQ-5D	Mean EQ-5D utility	0.62 (0.24) Average EQ-5D score at the last measure was significantly higher in patients receiving temsirolimus compared with IFN-α: by 0.10 on EQ-5D index (p=0.0279)
Zbrozek 2010 (143)	Global ARCC study	Patients with advanced RCC who had not received prior systemic therapy	*Global ARCC trial* Temsirolimus alone (administered SC starting with three MU three times per week for the first week, and increasing to a maximum of 18 MU three times per week by the third week IFN-α alone (25mg/30-minute IV infusion once weekly Combination of Temsirolimus & IFN- α (IV	EQ-5D questionnaires were obtained from 260 patients upon progression, and from 230 after a grade 3 or 4 AE, and from 278 in the TWIST state	EQ-5D (baseline, week 12, week 32 and whenever a grade 3/4 AE occurred, or at the time of disease progression or withdrawal from the study. The questionnaires, except for baseline attributed to one of the health	Baseline-temsirolimus (median)	0.689
						Baseline- IFN-α (median)	0.656
						Baseline-combination of temsirolimus & IFN-α	0.689
						Time with serious toxicity (TOX) (median)	0.585
						Time after progression (REL) (median)	0.587

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility score
			temsirolimus 15mg/30-minute infusion weekly plus 3 MU IFN- α three times weekly for week 1 and 6 MU SC three times weekly thereafter		states)	TWiST (median) * EQ-5D scores were pooled across all treatment groups for each of the three health states	0.689

Abbreviations: AE, adverse event; ARCC, advanced renal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; FACT-G, Functional Assessment of Cancer Therapy – General; FKSI, Functional Assessment of Cancer Therapy-Kidney Symptom Index ; IFN-α, interferon alpha; IL-2, interleukin 2; ILSM, least squares mean; mRCC, metastatic renal cell carcinoma; MU, million units; SC, subcutaneous; SD, standard deviation; PPE, palmar-plantar erythrodysaesthesia (hand-foot syndrome); PS, performance status; QoL, quality of life; RCC, renal cell carcinoma; TTO, time trade-off; TWIST, Time Without Symptoms or Toxicity; VAS, visual analogue scale.

10.12.10 *Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.*

The following differences were noted:

- Utility scores at baseline and following disease progression were higher in Castellano et al, 2009 (136), Cella et al 2011 (49) and Cella 2010 (137) compared with baseline and progression scores from the AXIS trial (see Table 42 for the utility values from the AXIS trial used in the model). This may be due to the fact that patients in the these three studies had received no prior treatment and would therefore be less likely to have experienced disease progression compared with patients from the AXIS trial, who had all experienced progression on prior therapy before enrolling in the study.
- Swinburn et al (2010) calculate disutility scores associated with mRCC for stable disease, progressed disease and various AEs commonly associated with first-line therapies (140). Members of the general public were asked to rate the different health states using the TTO method. The 'progressed disease' utility score reported in Swinburn et al was substantially lower than EQ-5D scores reported in the AXIS trial and all of the other studies identified in the systematic review (0.355). This may be due to differences in the type of study performed (societal preference vs clinical trial). As the AXIS trial reported EQ-5D scores, it was assumed that these would capture the impact of AEs associated with axitinib treatment and therefore an additional AE disutility was not applied to the model.
- Utilities in Uemura et al (2010) were reported as 'mean change from baseline' (141) and therefore could not be directly compared with scores from the axitinib clinical trial.
- Patients in Yang et al were treatment naïve with multiple poor prognostic factors (142) and therefore constituted a different patient population to those enrolled in the AXIS trial.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

Not applicable

10.13.1 ***The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:***

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***NHS EED***
- ***EconLIT***

[Response]

10.13.2 ***The date on which the search was conducted.***

[Response]

10.13.3 ***The date span of the search.***

[Response]

10.13.4 ***The complete search strategies used, including all the search terms textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).***

[Response]

10.13.5 ***Details of any additional searches, such as searches of company databases (include a description of each database).***

[Response]

10.13.6 ***The inclusion and exclusion criteria.***

[Response]

10.13.7 ***The data abstraction strategy.***

[Response]

10.14 Appendix 14: WinBUGS code for the fixed effects model (Section 6.7.5)

Continuous outcomes indirect comparison of HRs for PFS and OS

Fixed effects model

```
model{
#Fit data
    for(i in 1:N ){
        Lmu[i] < - d[Ltx[i]] - d[Btx[i]] + equals(arm[i],3)*sw[i]
        Lprec[i] < - 1/pow(Lse[i],2)
#Likelihood for mean differences between arms
        Lmean[i] ~ dnorm(Lmu[i],Lprec[i])
 #Calculate residual deviance for each i
        dev[i] <- (Lmean[i]-Lmu[i])* (Lmean[i]-Lmu[i])/pow(Lse[i],2)
        } # end i
# Check for good fit
        sumdev <- sum(dev[])
# adjustment for 3-arm trials
        sw[1]<-0
        for (m in 2:N) {
                sw[m] <- (Lmu[m-1] - d[Ltx[m-1]] + d[Btx[m-1]])/2
        }          # end m
#vague priors for basic parameters
        for (k in 1:NT){
                d[k]~dnorm(0,1.0E-6)
        } # end k
#Calculate pairwise HRs
        for (p in 1:(NT-1)){
        for (q in (p+1):NT){
                HR[p,q]<-exp(d[p]-d[q])
        } #end q
        } #end p
# Ranking and probability (125)
        for (l in 1:NT) {
                rk[l]<- rank(d[],l)
                best[l]<-equals(rk[l],1)
```

*} # **end l***

*} #**end model***

10.15 Appendix 15: Systematic review to identify RCTs and non-RCTs reporting efficacy and safety data for patients with mRCC who received BSC following progression with first-line sunitinib treatment.

The clinical search described in Section 6.1 and Section 6.2 was also designed to identify eligible studies for comparator interventions, relevant to the decision problem.

A further systematic review was conducted to identify clinical studies (RCTs and non-RCTs) which reported efficacy and safety data in patients with mRCC who received BSC following progression with first-line sunitinib treatment.

10.15.1 *Databases searched*

The following databases were searched via OVID:

- The Cochrane library incorporating:
  - The Cochrane Database of Systematic Reviews (Cochrane Reviews)
  - The Database of Abstracts of Reviews of Effects (DARE)
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
- The Health Technology Assessment Database (HTA)
- Ovid MEDLINE(R) In-Process and other non-indexed citations and Ovid MEDLINE(R) 1954 to present
- Ovid EMBASE 1980 to present day

10.15.2 *Date on which the search was conducted*

The searches were performed on 14th March 2012

10.15.3 *Date span of the search*

Please see Section 10.15.1

10.15.4 *Search strategy*

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: accessed March 14th 2011

# ▲	Searches	Results
1	exp Carcinoma, Renal Cell/	19121
2	exp Kidney Neoplasms/	51921
3	((renal or kidney) adj3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	60279

4	(sunitinib or su?10398 or su ?10398 or sutent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2061
5	(hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1227
6	Randomized controlled trials as Topic/	77575
7	Randomized controlled trial/	321733
8	Random allocation/	73414
9	Double blind method/	113240
10	Single blind method/	15798
11	Clinical trial/	467295
12	exp Clinical Trials as Topic/	250497
13	or/6-12	805089
14	(clinic$ adj trial$1).tw.	173596
15	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	114324
16	Placebos/	30564
17	Placebo$.tw.	138364
18	Randomly allocated.tw.	14042
19	(allocated adj2 random).tw.	683
20	or/14-19	354494
21	13 or 20	923823
22	Case report.tw.	175412
23	Letter/	751072
24	Historical article/	280300

25	Review of reported cases.pt.	0
26	Review, multicase.pt.	0
27	or/22-26	1196419
28	21 not 27	897824
29	Epidemiologic studies/	5256
30	exp case control studies/	538874
31	exp cohort studies/	1151226
32	Case control.tw.	61239
33	(cohort adj (study or studies)).tw.	61110
34	Cohort analy$.tw.	2761
35	(Follow up adj (study or studies)).tw.	33352
36	(observational adj (study or studies)).tw.	31717
37	Longitudinal.tw.	113511
38	Retrospective.tw.	217310
39	Cross sectional.tw.	126235
40	Cross-sectional studies/	135532
41	or/29-40	1569844
42	28 or 41	2282155
43	1 or 2 or 3 or 5	62701
44	4 and 42 and 43	470
45	(progress* or fail*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1384354
46	(interleukin 2 or bioleukin or IL-2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary	65821

	concept, unique identifier]	
47	((alpha adj2 interferon) or alferon or cilferon or kemron or veldona).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	33769
48	cytokine*.mp.	227979
49	4 or 46 or 47 or 48	299334
50	45 and 49	44068
51	4 or 50	45356
52	42 and 43 and 51	937

Embase 1974 to 2012 March 13: accessed March 14th 2012

# ▲	Searches	Results
1	exp kidney carcinoma/	36364
2	exp kidney tumor/	79199
3	((renal or kidney) adj3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	83974
4	(hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1428
5	exp sunitinib/	8078
6	(sunitinib or su?10398 or su ?10398 or sutent).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	8276
7	Clinical trial/	829354
8	Randomized controlled trial/	301140
9	Randomization/	55939

10	Single blind procedure/	14912
11	Double blind procedure/	105956
12	Crossover procedure/	32114
13	Placebo/	206752
14	Randomi?ed controlled trial$.tw.	69587
15	Rct.tw.	8689
16	Random allocation.tw.	1137
17	Randomly allocated.tw.	16622
18	Allocated randomly.tw.	1762
19	(allocated adj2 random).tw.	774
20	Single blind$.tw.	11885
21	Double blind$.tw.	128575
22	((treble or triple) adj blind$).tw.	284
23	Placebo$.tw.	171762
24	Prospective study/	184458
25	or/7-24	1200804
26	Case study/	15038
27	Case report.tw.	224712
28	Abstract report/ or letter/	830002
29	or/26-28	1065466
30	25 not 29	1166325
31	Clinical study/	82089
32	Case control study/	58059
33	Family study/	9506

34	Longitudinal study/	48811
35	Retrospective study/	252975
36	Prospective study/	184458
37	Randomized controlled trials/	13617
38	36 not 37	184118
39	Cohort analysis/	110970
40	(Cohort adj (study or studies)).mp.	74313
41	(Case control adj (study or studies)).tw.	57392
42	(follow up adj (study or studies)).tw.	40153
43	(observational adj (study or studies)).tw.	40900
44	(epidemiologic$ adj (study or studies)).tw.	63412
45	(cross sectional adj (study or studies)).tw.	56687
46	or/31-35,38-45	898177
47	1 or 2 or 3 or 4	95749
48	30 or 46	1832109
49	5 or 6	8276
50	47 and 48 and 49	1919
51	(progress* or fail*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1728718
52	(interleukin 2 or bioleukin or IL-2).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	92457
53	((alpha adj2 interferon) or alferon or cilferon or kemron or veldona).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	54496
54	cytokine*.mp.	318075

55	49 or 52 or 53 or 54	419894
56	51 and 55	66249
57	49 or 56	71150
58	47 and 48 and 57	2614

Cochrane Library: accessed March 14th 2012

ID	Search	Hits
#1	MeSH descriptor **Carcinoma, Renal Cell** explode all trees	390
#2	MeSH descriptor **Kidney Neoplasms** explode all trees	569
#3	(renal or kidney) NEAR/3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumo?r*)	1126
#4	hypernephroma* or nephroid carcinoma* or hypernephroid carcinoma*	8
#5	sunitinib or su?10398 or su ?10398 or sutent	107
#6	(**#1** OR **#2** OR **#3** OR **#4**)	1143
#7	(#5 AND #6)	61
#8	progress* or fail*	73558
#9	interleukin 2 or bioleukin or IL-2	5253
#10	(alpha NEAR/2 interferon) or alferon or cilferon or kemron or veldona	4088
#11	cytokine*	5241
#12	(#5 OR #9 OR #10 OR #11)	12168
#13	(#8 AND #12)	2567
#14	(#5 OR #13)	2621
#15	(#6 AND #14)	203†

[†]One Cochrane group, so 202 citations exported

10.15.5 *Additional searches*

The following conference abstracts were also reviewed:

- American Society of Clinical Oncology (ASCO)
- ASCO-Genitourinary (ASCO-GU)
- European Society for Medical Oncology (ESMO)
- European Conference for Clinical Oncology (ECCO)

These searches were restricted to abstracts published from 2007 and onwards.

In addition, the following were also searched

- clinicaltrials.gov
- National Cancer Institute (NCI) clinical trial database
- ISRCTN register
- United Kingdom Coordinating Committee on Cancer Research (UKCCR) register of cancer trials
- European Organisation for Research and Treatment of Cancer (EORTC)
- UK clinical trials gateway
- metaRegister (mRCT) of controlled trials

10.15.6 *The inclusion and exclusion criteria.*

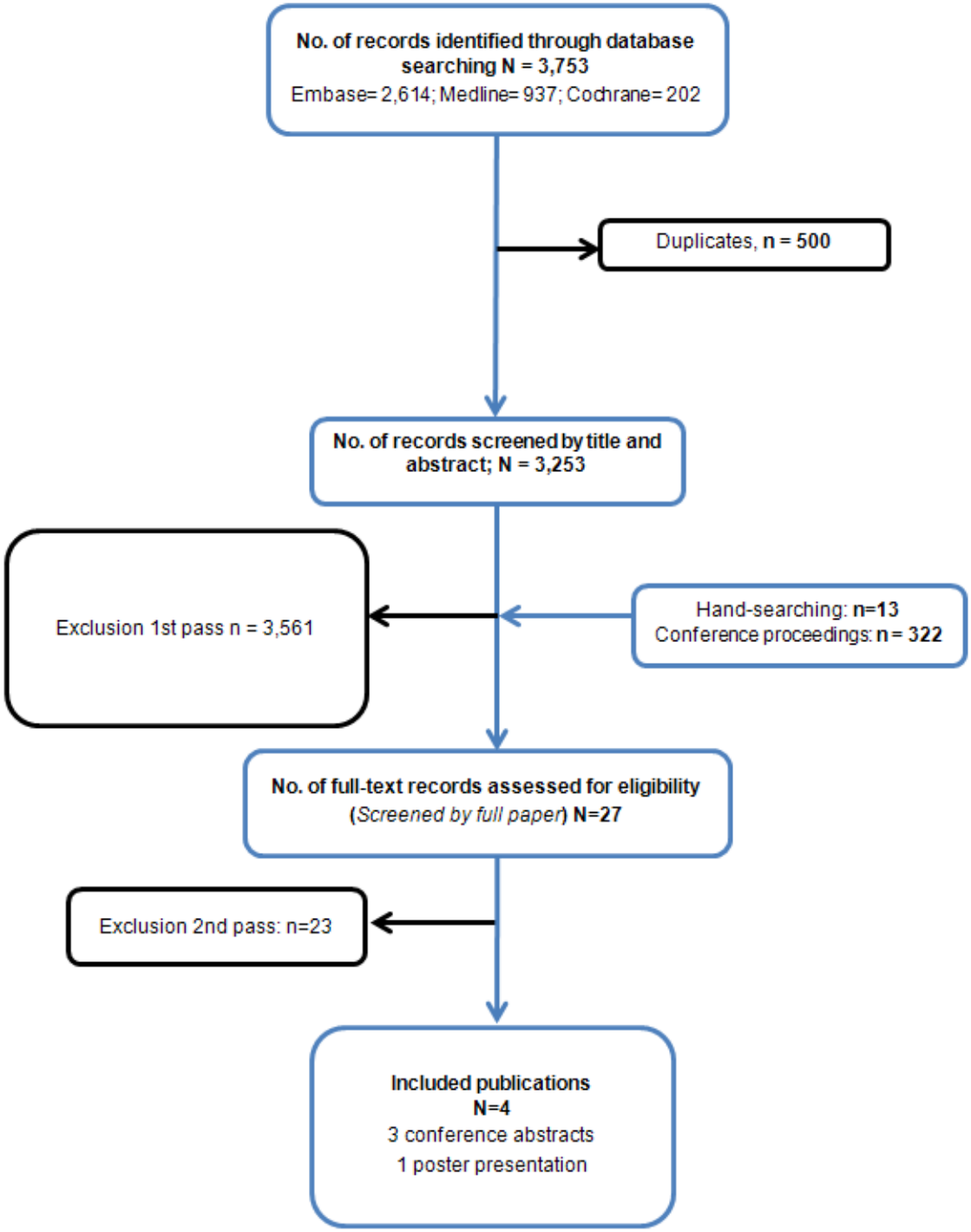
Inclusion criteria	
Population	Adult patients with metastatic RCC
Age	≥ 18 years
Gender	No restrictions
Race	No restrictions
Outcomes	Including but not restricted to: Overall survival (OS) Progression-free survival (PFS) Time to progression (TTP) Survival after progression (SAP) Survival measures that reported on 1st and 2nd line treatment were collected
Interventions	First-line therapy: Sunitinib Cytokine therapy (IL-2, IFNa) Second-line therapy:

	Best supportive care†
Comparators	No restrictions
Study design	Prospective, randomised controlled trials Prospective non-randomised controlled studies
Language	No restrictions

†There is currently no standard definition of what treatments constitute best supportive care. A commonly used definition is 'any palliative therapeutic modality that may be offered to the patient excluding chemotherapy but including radiotherapy and non-cytotoxic medication'. This includes antibiotics, analgesics, antiemetics, corticosteroids, blood transfusions, nutritional support and focal external-beam radiation for control of pain, cough, dyspnoea or haemoptysis.

10.15.7 *The data abstraction strategy.*

Identified studies were independently assessed by a reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria. Any uncertainties were resolved by a second reviewer. Data were extracted from eligible publications into a pre-defined table by a reviewer and verified by a second reviewer.



All studies identified were retrospective analyses and as none were available as full text publications, there was limited data available for abstraction.

10.16 Appendix 16: Simulated treatment comparison

Calibrating the equations to derive comparison measure (δ):

Comparisons between axitinib vs. BSC and axitinib vs. everolimus were derived by calibrating the axitinib-based PFS and OS equations to the median values described above. Using the mathematical properties of the log-normal and Weibull distributions, the values of the comparison measure δ can be calculated algebraically. The details of these calculations are as follows:

Calibration of Lognormal Equation

The survival distribution is given by

$$(1)\ S(t,x) = 1 - \Phi\left(\left[\frac{\log(t)-\mu}{\sigma}\right]\right)$$

Where Φ^{-1} is the cumulative distribution function (cdf) of the normal distribution with mean μ and standard deviation σ,

The scale parameter is depends on characteristics $\mathbf{X}$ and expressed as follows: $\mu = X\beta$,

where β is a vector of prognostic factors

Assuming BSC/everolimus and axitinib all follow a log-normal distribution with a common σ and setting $S(t,x) = 0.5$, μ_c for everolimus can be computed as:

$$(2)\ \mu_c = [\ln(t_c) - \sigma * \Phi^{-1}(0.5)]$$

Where t_c is the median OS or PFS for everolimus/BSC (i.e., 54.4 or 16.9 weeks) and σ is the standard deviation estimated from axitinib equations (1),

The adjustment factor is then calculated as:

$$(3)\ \hat{\delta} = \mu_c - \bar{X}_c\hat{\beta}'$$

Where $\bar{X}_c\hat{\beta}$ is calculated at the mean values of $\mathbf{X}$ (predictors in risk equations) for everolimus patients with prior sunitinib in the RECORD-1 trial.

The adjustment factor is then plugged in to the AXIS intercept only equation so that OS and PFS curves are predicted for axitinib like patients who failed sunitinib had they received BSC/everolimus in the AXIS trial

$$(4)\ S(t,x) = 1 - \Phi\left(\left[\frac{\log(t) - (\mu+\delta)}{\sigma}\right]\right)$$

Calibration of Weibull Equation

The OS and PFS equations derived from the AXIS trial relate the hazard rate (α) to patient characteristics:

$$(1)\ \alpha = \exp(-(X\beta) * \gamma)'$$

Where X is a vector of predictors, β is a vector of unknown parameters and γ is the shape parameter. The survival distribution is then given by

$$(2)\ S(t, x) = \exp(-\alpha * t^{\gamma})$$

Where α implicitly depends on $\mathbf{X}$.

Assuming BSC/everolimus and axitinib arm follow the same survival distribution and S (t,x)= 0.5, alpha for BSC/everolimus can be computed as:

$$(3)\ \alpha_c = \frac{-\ln(0.5)}{t_c^{\gamma}},$$

Where t_c is the median OS or PFS for BSC/everolimus (i.e., 54.4 or 16.9 weeks) and γ is the shape parameter from axitinib equations (1),

Alpha for BSC/everolimus is also given by:

$$(4)\ \alpha_c = \exp(-(\bar{X}_c\hat{\beta} + \delta) * \gamma)'$$

The adjustment factor is then calculated by combining equation 3 and 4 as

$$(5)\ \hat{\delta} = \frac{-\ln(\alpha_c)}{\gamma} - \bar{X}_c\hat{\beta}.$$

Where, $\bar{X}_c\hat{\beta}$ is calculated at the mean values of $\mathbf{X}$ (predictors in risk equations) for everolimus patients with prior sunitinib in the RECORD-1 trial.

Using the STC Results in Economic Modelling

The results from the STC analyses (i.e., estimates of δ) were used to derive predicted PFS and OS curves for everolimus and BSC for use in the economic model. PFS and OS for axitinib were predicted from log-normal and Weibull equations that included an intercept only (since the economic model was Markov-based). The corresponding δ values were applied as follows, to generate predictors for comparators:

For log-normal equations: $S(t) = 1 - \Phi([\log(t) - (\mu + \delta)]/\sigma)$

For weibull equations: $S(t) = \exp(-\exp(-(\text{intercept} + \delta)*\gamma)*t^{\gamma})$

10.17 Appendix 17: RENCOMP supporting data

Table 69: Dosing, number of prescriptions and treatment length with first-line sunitinib

		Count	Mean	Standard Deviation	Median	Min	Max
Number of prescriptions of sunitinib	BSC	76	5.1	5.1	3	1	33
	SOR	59	8.2	6.3	6	1	26
Total number of days of sunitinib treatment (approx)	BSC	76	170.2	169.7	100	33	1100
	SOR	59	272.3	210.0	200	33	867
Mean_dose_sunitinib	BSC	76	34.8	13.2	29.2	12.5	50.0
	SOR	59	31.2	12.7	25.0	18.1	50.0
Total_dose_sunitinib	BSC	76	158.9	158.7	100.0	25.0	962.5
	SOR	59	219.3	151.0	175.0	25.0	800.0

Abbreviations: BSC, best supportive care; SOR, sorafenib.

Table 70: Dosing of first-line sunitinib

	BSC		Sorafenib	
	Count	%	Count	%
Sunitinib 12.5 mg	90	23.2	161	33.4
Sunitinib 25 mg	158	40.7	205	42.5
Sunitinib 50 mg	140	36.1	116	24.1

Abbreviations: BSC, best supportive care.

Table 71: Resource use

		Count	Mean	St. dev.	Median	Min	Max
mrcc_inpatient_days	BSC	76	32.5	78.4	14	0	592
	SOR	59	13.9	20.9	4	0	98
mrcc_outpatient_days	BSC	76	8.2	7.9	6	0	39
	SOR	59	7.9	5.8	7	0	26

Abbreviations: BSC, best supportive care; SOR, sorafenib.

Table 72: Means and medians for survival time (days)

Second-line treatment	Mean				Median			
	Estimate (days)	Std. Error	95% CI		Estimate (days)	Std. Error	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
BSC	289.364	34.822	221.113	357.614	176.000	29.484	118.211	233.789
Sorafenib	410.146	52.781	306.694	513.597	280.000	61.905	158.666	401.334
BSC + sorafenib	346.726	31.406	285.170	408.281	218.000	27.940	163.237	272.763

Abbreviations: BSC, best supportive care; CI, confidence interval.

Table 73: Sensitivity analysis, HR for sorafenib vs BSC for different models

Model	Base case	2	3	4	5	6	7	8
Sorafenib vs BSC	0.621‡	0.652†	0.580‡	0.712	0.615‡	0.596‡	0.665†	0.594‡
Gender (female vs. male)	X	X	X	X	X	X	X	X
Age at 2nd line treatment start (age ≥ 65 vs age<65)	X	X	X	X	X	X	X	X
Nephrectomy (yes vs. no)	X	X	X	X	X	X	X	X
Lead time between RCC and mRCC (≥ 1 year vs <1 year)	X	X	X	X	X	X	X	X
Days since mRCC diagnose and start of systematic treatment with sunitinib (<1 year vs ≥ 1 year)		X	X				X	
Days of sunitinib treatment (≥ 90 days vs < 90 days)		X		X			X	
Region		X			X			X
Institution size (large vs. small)		X				X		X

Abbreviations: BSC, best supportive care; HR, hazard ratio mRCC, metastatic renal cell carcinoma; RCC, renal cell carcinoma.

†Statistically significant at 5% level; ‡Statistically significant at 10% level.

10.18 Appendix 18: Non-RCT evidence

Summary of axitinib efficacy from Phase II studies (A4061012, A4061023, A4061035)

- Three Phase II, open-label, single-arm studies were conducted to assess the efficacy and safety of axitinib in patients with mRCC that had failed at least one previous systemic treatment.
  - Study A4061012 and A4061035 were conducted in patients who had received first-line cytokine therapy; A4061012 was conducted in the USA and Europe and A4061035 was conducted in Japan.
  - Study A4061023 was a US based study, conducted in patients who had failed prior-sorafenib therapy with no upper limit on the number of previous failed therapies.
- In all three studies, axitinib was administered at a dose of 5 mg BD, with the option to increase or decrease the dose depending on AEs experienced by individual patients.
- For studies A4061012, A4061023 and A4061035:
  - The primary outcome of ORR was 44.2%, 22.6% and 50%, respectively.
  - Median response duration was 23 months, 17.5 months and 11.5 months, respectively.
  - For studies A4061012 and A4061023, median OS was 29.9 months and 13.6 months, respectively.
  - For studies A4061023 and A4061035, PFS was 7.4 months and 11.0 months, respectively.

A systematic review was conducted to identify non-RCTs reporting on the efficacy and safety of axitinib. Please refer to Sections 6.1 and 6.2 for the full details.

Critical appraisal of relevant non-RCTs

A critical appraisal of the non-RCT studies included can be found in Section 10.7 (Appendix 7).

Relevant non-RCTs

Study A4061012 (52, 71)

A summary of the methodology of study A4061012 is presented in Table 74.

Table 74: Methodology - Study A4061012

	Details
Objective	To assess the efficacy and safety of axitinib in patients with mRCC who had failed on previous cytokine-based treatment.
Location	USA, France and Germany (www.clinicaltrials.gov.uk/ct/show/NCT00076011)

	Details
Design	A Phase II, open-label, international, single arm, multicentre study.
Duration of study	3rd October 2003 – 7th April 2004. Treatment with axitinib was continued until progressive disease, unacceptable toxicity or withdrawal of consent occurred.
Main inclusion criteria	• Histologically proven mRCC • Failure of 1 previous cytokine-based treatment regimen (IFNα, IL-2 or both) • ≥ 1 RECIST-defined target lesion that had not been irradiated • Adequate haematological, hepatic, renal and cardiac function • Urinary protein < 2+ by urine dipstick (or quantitative urinary protein less than 2g/24h • ECOG PS of 0 or 1.
Main exclusion criteria	• Previous treatment with anti-angiogenic drugs (including thalidomide) • Pre-existing uncontrolled hypertension (>140/90 mmHg with medication) • Treatment for peptic ulcer in the last 6 months • Active GI bleeding • Malabsorption • Active seizures or brain metastases • History of another malignancy in the past 5 years with the exception of non-melanoma skin cancer or *in-situ* cervical or breast cancer • Major surgery or radiotherapy within 4 weeks of starting study treatment.
Intervention	Axitinib was administered at a starting dose of 5 mg BD. Dose interruption was permitted for patients who developed Grade 4 haematological toxicity, or other non-haematological grade 3, grade 4, or subjectively intolerable grade 2 toxicity that could not be controlled. If resolution did not occur within 4 weeks, the patient was withdrawn from the study. Dose decreases were non-reversible. If no toxicity of Grade 2 or higher occurred during 8 weeks of treatment and no tumour response was recorded, the dose was titrated upward by 20%.
Permitted and disallowed concomitant medications	Inhibitors or inducers of CYP3A4 were not permitted. Antacid medications were not permitted. Antihypertensive medications were permitted.
Discontinuation of study therapy	Patients continued study treatment until they experienced progressive disease, unacceptable toxicity or until they withdrew consent.
Assessments	Physical examinations and laboratory tests were conducted at baseline and repeated every 4 weeks. Tumour assessments by physical examination and radiological methods (i.e. CT) were done by the Investigator at baseline and every 8 weeks using RECIST criteria. CR or PR requires confirmation at least 4 weeks after the response was first noted. Patients measured their own blood pressure every day and recorded the results.
Primary outcomes	ORR (% patients with confirmed CR or PR according to RECIST criteria).
Secondary outcomes	Duration of response, stable disease, time-to-progression, OS, safety, pharmacokinetics and HRQoL (EORTC QLQ-C30).
Analysis populations	The analyses were conducted on the ITT population – all patients that received at least 1 dose of study medication.
Statistical	Sample size was established using a 2-stage minimax Simon's design top

	Details
methods	evaluate the null hypothesis that the true ORR was 5% and the alternative hypothesis that the ORR was 15% or higher, with a type I error (α) level of 0.05 and type II error (β) of 0.20.
Duration of follow-up	Patients were followed until they experienced progressive disease, unacceptable toxicity or until they withdrew consent.

Abbreviations: BD, twice-daily; CR, complete response; CT, computed tomography; CYP3A4, cytochrome P450 3A4; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-30; European Organisation for Research and Treatment of Cancer Quality of life questionnaire version 3.0; GI, gastrointestinal; mmHg, millimetres of mercury; HRQoL, health-related quality of life; IFNα, interferon alpha; IL-2, interleukin-2; ITT, intent-to-treat; mRCC, metastatic renal cell carcinoma; mg, milligrams; ORR, objective response rate; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TTP, time to progression.

Baseline characteristics, patient disposition and treatment duration: Study A4061012

The baseline characteristics for patients enrolled in study A4061012 are presented inTable 75. In total, 52 patients were enrolled, of which all received at least one dose of study medication (the ITT population). The median duration of axitinib treatment was 9.4 months (range 0.1-32.0) and the mean daily dose was 8.83 mg (range 3.9-11.7). Dose reduction was performed in 15 (28.8%) patients due to Grade 3 AEs. In total, 6 (11.5%) patients received axitinib doses above 5 mg BD. At the time of report preparation, 51 patients (98%) had discontinued from the study. Reasons for treatment discontinuation were; death (1 patient), non-fatal treatment-related AEs (10 patients), progressive disease or absence of efficacy (25 patients), withdrawal of consent (1 patient), study terminated by sponsor (3 patients) and unknown reasons (11 patients).

Table 75: Baseline characteristics - Study A4061012

	Patients (N=52)
Age, years	
Median, range	59 (35–85)
Sex, n	
Male	40
Female	12
Performance status, n	
0	31
1	21
Previous systemic treatment	
Cytokine	52
IFN alone	27
IL-2 alone	9
IFN and IL-2	8
Cytotoxic chemotherapy	8
Previous radiotherapy	10
MSKCC risk factors for second-line treatment	
0	22
≥ 1	30

Abbreviations: IFN, interferon, IL-2, interleukin-2; MSKCC, Memorial Sloan-Kettering Cancer Centre.

Results: Study A4061012

Primary endpoint – objective response

In total, 2 (4%) patients had a complete response and 21 (40%) patients had a partial response, giving an ORR of 44.2% (95% CI 30.5-58.7) based on RECIST criteria (see Table 10).

Secondary efficacy endpoints

Duration of response: The median DR was 23.0 months (95% CI 20.9-not estimable).

Stable disease: SD was noted in 42% of patients for 8 weeks or longer and in 25% of patients for 24 weeks or longer

Time to progression: After a median survival follow-up of 31 months (range 10.6-35.8), 38 patients had progressed or died. The median time to progression was 15.7 months (95% CI 8.4-23.4)

Overall survival: At the time of the final analysis (January 2007), median OS was 29.9 months (95% CI 20.3-not estimable). The 1-year survival rate was 78.8% (95% CI 67.7-89.9).

Five-year OS data were collected in December 2009. The 5-year survival rate was 20.6% (95% CI 10.9-32.4) (67).

HRQoL: There was minimal change from baseline in QoL as measured by the European Organisation for Research and Treatment of Cancer Quality of life questionnaire version 3.0 (EORTC QLQ-C30) over 40 weeks. Fatigue and appetite loss increased slightly over the course of the study and diarrhoea increased particularly between Weeks 16–40.

Study A4061023 (42, 72)

A summary of the methodology of study A4061023 is presented in Table 76.

Table 76: Methodology - Study A4061023

	Details
Objective	To investigate the efficacy and safety of axitinib in patients with sorafenib-refractory mRCC
Location	Multiple sites in the USA http://www.clinicaltrials.gov/ct2/show/NCT00282048
Design	A Phase II, open-label, single-arm, multicentre study.
Duration of study	Patients received axitinib treatment until disease progression or unmanageable toxicity occurred, or consent was withdrawn.
Main inclusion criteria	• Patients ≥ 18 years • Histologically documented mRCC (any subtype) • Prior nephrectomy • Prior failed treatment with sorafenib • One or more RECIST-defined target lesions that had not been irradiated • ECOG PS ≤ 1 • Adequate organ function.
Main exclusion criteria	• Gastrointestinal bleeding; • Pre-existing uncontrolled hypertension (<140/90 mm Hg); • Malabsorption; • Uncontrolled brain metastases; • Major surgical procedure or radiation therapy within 4 weeks of beginning study treatment.
Intervention	The starting dose of axitinib was 5 mg BD with food. The dose was increased in a step-wise fashion from 5 mg BD to 7 mg BD, then to 10 mg BD if patients did not experience toxicity >Grade 2 for a continuous 2-week period, and in the absence of hypertension (defined as 2 BP measurements of <150/90 mmHg taken in the clinic < 1 hour apart) at any point during the study. Dose interruption and/or reduction to 3 mg BD, then 2 mg BD was allowed for patients who developed Grade 4 haematologic toxicities or Grade 3 or 4 non-haematologic toxicity. Dose interruption was performed in patients with >2 g proteinuria per 24 hours. Treatment was restarted at a lower dose when total protein and creatinine clearance were <2 g proteinuria per 24 hours.
Permitted and disallowed concomitant medications	Antihypertensive medications were permitted. There was no limit on the number of prior failed systemic therapies.
Discontinuation of study therapy	Patients discontinued treatment due to insufficient clinical response or disease progression, AEs, withdrawal of consent and other causes (not specified).
Assessments	Tumour response was assessed at baseline and every 8 weeks according to RECIST. Physical examination and laboratory tests were assessed at baseline, every 4 weeks and at follow-up (28 days after the last dose).
Primary outcomes	ORR (percentage of patients with CR or PR as measured by RECIST criteria).
Secondary outcomes	Safety, duration of response, PFS, OS and patient reported outcomes (FKSI) and FKSI-DRS).

	Details
Analysis populations	Analyses were performed on all patients that received at least 1 dose of study medication.
Statistical methods	The study required 62 patients to test the null hypothesis that the response rate to axitinib in sorafenib-refractory mRCC was 8% or less vs an alternative hypothesis that the response rate was 20% or greater, which was considered indicative of activity in this patient population and worthy of additional study. In the event of at least 9 responses, the null hypothesis would be rejected with a target α error rate of 0.10; with 8 or fewer responses the alternative hypothesis would be rejected with a target β error rate of 0.10.
Duration of follow-up	Follow-up assessments were performed 28 days after the final dose. Patients were followed until disease progression, unmanageable toxicity, or withdrawal of consent occurred.

Abbreviations: AE, adverse event; BD, twice daily; BP, blood pressure; CTEAE, Common Terminology Criteria for Adverse Events ; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IFNα, interferon alpha; IL-2, interleukin-2; GI, gastrointestinal; mmHg, millimetres of mercury; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

Baseline characteristics, patient disposition and duration of treatment: Study A4061023

The baseline characteristics of patients that entered study A4061023 are presented in Table 77. Patients received a median of 6.2 months of axitinib treatment (range, 0.2-33.2 months). The dose was titrated to > 5 mg BD in 33 patients (53.2%; median duration of escalation, 9.4 weeks; escalation duration range, 2-141.9 weeks). Twenty (32.3%) and 13 (21.0%) patients experienced dose titration to 7 mg BD (median duration, 7.5 weeks) and to 10 mg BD (median duration, 11.0 weeks), respectively. Dose modifications to < 5 mg BD for at least 1 week occurred in 11 patients (17.7%; median duration, 10.0 weeks). The lowest daily dose was 2 mg BD; the highest daily dose was 10 mg BD. Patients discontinued treatment due to insufficient clinical response or disease progression (n=30); AEs (n=22); withdrawal of consent (n=1); and other causes (n=8). At the time of the analysis, three patients were still taking axitinib.

Table 77: Baseline characteristics: Study A4061023

	Total patients enrolled N=62
Age, years	
Median, range	60 (35-77)
Sex, n	
Male	42
Female	20
Performance status, n	
0	21
1	41
Previous systemic treatment, n (%)	
Sorafenib	62 (100)
Sunitinib	14 (22.6)
Cytokine therapy	38 (61.3)
Cytotoxic therapy	12 (19.4)
Bevacizumab	5 (8.1)
Temsirolimus	3 (4.8)
Other	18 (29.0)
Number of prior systemic treatment regimens, n (%)	
1†	16 (25.8)
2	16 (25.8)
3	16 (25.8)
4	6 (9.7)
≥ 5	8 (12.9)
Number of prior antiangiogenic treatments, n (%)	
1	44 (71.0)
≥ 2	18 (29.0)
Prior nephrectomy, n (%)	62 (100)

† Patients treated with 1 prior regimen were those that received only sorafenib.

Results: Study A4061023

Primary endpoint – objective response rate

The ORR was 22.6% (95% CI, 12.9%-35.0%); in total 14 patients achieved a partial response according to RECIST.

Secondary efficacy endpoints

Duration of response: The median DR was 17.5 months (95% CI, 7.4-not estimable). In total, 17.7% of patients achieved stable disease.

Stable disease: An additional 11 patients (17.7%) experienced SD.

Progression-free survival: The mean PFS for the whole population was 7.4 months (95% CI, 6.7-11.0), with a median follow-up of 22.7 months.

Overall survival: Median OS was 13.6 months (95% CI, 8.4-18.8).

Patient reported outcomes: After 20 weeks of study treatment, QoL data were available for 33 patients. Mean FKSI scores significantly decreased from baseline to 20 weeks (mean change, -5.2; 95% CI -8.7 to -2.28; $p<0.001$) as did FKSI-DRS (mean change, -2.6; 95% CI, -4.34 to -0.87; $p<0.005$). The median time to deterioration in health status, which was defined as death, progression or a worsening of at least six points on the FKSI-15 total score, was 96 days (95% CI, 52-140 days).

Study A4061035 (53)

A summary of the methodology for study A4061035 is described in Table 78.

Table 78: Methodology – Study A4061035

	Details
Objective	To investigate axitinib efficacy, safety and biomarkers in Japanese patients with cytokine-refractory mRCC.
Location	Japan
Design	Open-label, Phase II, multicentre study.
Duration of study	1 year
Main inclusion criteria	• Age ≥ 20 years • Histologically confirmed mRCC with a clear cell component • ≥ 1 target lesion defined by RECIST • Prior nephrectomy • Refractory to first-line cytokine therapy (IFNα and/or IL-2) • ECOG PS of 0 or 1 • Adequate bone marrow, hepatic and renal function • Baseline proteinuria <2+ by urine dipstick or <2 g/24h urine collection • BP ≤ 140/90 mmHg (antihypertensive medications permitted)
Main exclusion criteria	• Clinically relevant GI disorders with the potential to affect ingestion or absorption • Active seizure disorders • Evidence of brain metastases, spinal cord compression or carcinomatous meningitis • Myocardial infarction • Severe or unstable angina • Coronary or peripheral arterial bypass graft • Symptomatic congestive heart failure or cerebrovascular accident ≤ 12 months prior to study medication
Intervention	Axitinib 5 mg BD with food. The axitinib dose could be increased to 7 mg BD and then to a maximum of 10 mg BD in patients with no Grade >2 treatment-related AE and with ≤ 150/90 mmHg for ≥ 2 weeks without the use of anti-hypertensive medication. The medication dose was reduced to 3 mg BD and then to 2 mg BD in patients who developed Grade 3 treatment-related, non-haematologic AEs and patients with 2 readings of systolic BP >150mmHg or diastolic BP >100 mmHg who were receiving maximal anti-hypertensive therapy. Patients with Grade 4 treatment-related AEs, 2readings of systolic BP >160 mmHg or diastolic BP >105 mmHg, or ≥ 2 g protein/24 h had their dose interrupted. Treatment was resumed at 1 lower dose level when AEs improved to grade ≤ 2, BP was <150/100 mmHg or <2 g protein/24 h was present.
Permitted and disallowed concomitant medications	Antihypertensive medications were permitted.
Discontinuation of study	The axitinib dose was interrupted in patients with Grade 4 treatment-related AEs, 2 readings of systolic BP >160 mmHg or diastolic BP >105 mmHg or ≥

	Details
therapy	2 g protein/24 h.
Assessments	Tumours were radiologically assessed before treatment was started and every 8 weeks thereafter according to RECIST by the Investigator and an IRC. AEs were assessed according to CTCAE criteria.
Primary outcomes	ORR (percentage of patients with CR or PR as measured by RECIST criteria).
Secondary outcomes	PFS, duration of response, stable disease, safety, biomarkers
Analysis populations	All patients that received at least one dose of axitinib were included in the efficacy and safety analyses.
Statistical methods	A total of 63 patients were required to test the null hypothesis that the true ORR was ≤ 10% vs the alternative hypothesis that the true ORR was ≥ 25% with a 1-sided α level of 5% and 90% power.
Duration of follow-up	The analysis was conducted 1 year after all patients (excluding those who had discontinued treatment) initiated axitinib treatment.

Abbreviations: AE, adverse event; BD, twice daily; BP, blood pressure; CTEAE , Common Terminology Criteria for Adverse Events ; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IFNα, interferon alpha; IL-2, interleukin-2; GI, gastrointestinal; mmHg, millimetres of mercury; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

Baseline characteristics, patient disposition and duration of treatment: Study A4061035

The baseline characteristics of patients that participated in study A4061035 are presented in Table 79. The median treatment duration with axitinib was 326 days (range, 13-696) with a mean daily dose of 7.1 mg (range, 1.6-16.4). Axitinib dosing was titrated >5 mg BD in five patients (8%), and reduced to <5 mg BD in 42 patients (66%). In total, 37 patients discontinued the study, 13 due to treatment-related AEs and 24 due to disease progression. As of the analysis cut-off date, 27 patients (42%) were still receiving axitinib.

Table 79: Baseline characteristics – Study A4061035

	Total patients enrolled N=64
Age, years	
Median, range	63 (34-80)
Sex, n	
Male	44
Female	20
Performance status, n	
0	57
1	7

Results: Study A4061035

Primary efficacy endpoint: objective response rate

The ORR was 50% (95% CI, 37.2-62.8) according to the IRC assessment. The ORR was 54.7% according to the Investigator's assessment.

Secondary efficacy endpoints

Duration of response: The median DR was 11.5 months (95% CI, 8.3-not estimable).

Stable disease: SD for ≥ 8 weeks was achieved by 29 patients (45.3%) according to the IRC assessment and 26 patients (40.6%) according to the Investigator's assessment.

Progression free survival: Median PFS was 11.0 months (95% CI, 9.2-12.0) according to the IRC assessment and 12.0 months (95% CI, 9.2-14.8) according to the Investigator's assessment.

10.19 Appendix 19: Extrapolation approach for the economic model

The following functional formulas were utilised to incorporate the parametric survival analysis results into the economic model.

Exponential distribution:

$$S(t) = e^{-\lambda t}.$$

$\lambda = e^{\beta}$, β is the constant output from STATA.

Parameter: rate (lambda: λ)

Lognormal distribution:

$$S(t) = 1 - \Phi\left(\frac{\ln t - \mu}{\sigma}\right),$$

$S = \ln \sigma$, S is the ln_sig output from STATA.

where Φ is the cumulative distribution function of the normal distribution

$$\left(\Phi(x) = \int_{-\infty}^{x} \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}t^2}\, dt\right).$$

Parameters: mean (mu: μ), standard deviation (sigma: σ).

Including hazard ratio to log normal distribution:

The log normal distribution is not a proportional hazard model but rather incorporates an accelerated failure time structure. This means a hazard ratio (HR) should not technically be applied to a log normal distribution. However, as sensitivity analysis in this model lognormal distribution as been used in several instances by applying an HR to create a modeled curve in the following way:

$$S_{BSC}(t) = S_{AXI}(t)^{\frac{1}{HR}} = \left(1 - \Phi\left(\frac{\ln t - \mu}{\sigma}\right)\right)^{\frac{1}{HR}}$$

where $S_{BSC}(t)$ is the survival function of the BSC arm, $S_{AXI}(t)$ is the survival function of theaxitinib arm, Φ is the cumulative distribution function of the normal distribution:

$$\left(\Phi(x) = \int_{-\infty}^{x} \frac{1}{\sqrt{2\pi}} e^{-\frac{1}{2}t^2}\, dt\right).$$

Parameters of axitinib survival curve: mean (mu: μ), standard deviation (sigma: σ) and HR is the hazard ratio of axitinib versus BSC.

Weibull distribution:

$S(t) = e^{(-\lambda t^{p})}$.(Eq 4)

$\lambda = e^{\beta}$, $P = \ln\ p$, β is the const and P is the ln_p output of STATA.

Parameters: constant (beta: β), shape (*p*)

Including hazard ratio to Weibull distribution:

The Weibull distribution is a proportional hazard function and thus allows the application of an HR to generate a modeled comparator curve. The following structure has been utilized to generate Weibull comparator curves in the axitinib model:

$$S_{BSC}(t) = e^{\left(-\lambda \cdot \frac{1}{HR} \cdot t^{p}\right)}$$

where $S_{BSC}(t)$ is the survival function of BSC arm,

Parameters of axitinib survival curve: constant (beta: β, $\lambda = e^{\beta}$), shape (*p,* $P = \ln\ p$), and HR is the hazard ratio of axitinib versus BSC.

Gompertz distribution:

$$S(t) = e^{\left(\frac{-\lambda}{\gamma} \cdot \left(e^{\gamma t} - 1\right)\right)}$$,(Eq 6)

$\lambda = e^{\beta}$, β is the const output of STATA.

Parameters: constant (beta: β), scale (gamma: γ)

Including hazard ratio to Gompertz distribution:

The Gompertz distribution is a proportional hazard function and again supports the application of an HR. The following structure has been utilized to generate Gompertz comparator curves in the axitinib model: :

$$S_{BSC}(t) = e^{\left(\frac{-\lambda_{BSC}}{\gamma} \cdot \left(e^{\gamma t} - 1\right)\right)}$$

where $S_{BSC}(t)$ is the survival function of BSC arm,

Parameters of axitinib survival curve: constant (beta: β, $\lambda_{AXI} = e^{\beta}$, $\lambda_{BSC} = e^{\beta + \frac{1}{HR}}$), shape (*p*, $P = \ln p$).

λ_{AXI} is the lambda parameter of axitinib survival curve, λ_{BSC} is the lamba parameter of BSC survival curve, andHR is the hazard ratio of axitinib versus BSC.

Loglogistic distribution:

$$S(t) = \frac{1}{1 + \lambda * t^{\frac{1}{\gamma}}}, \qquad \text{(Eq 8)}$$

$G = \ln \gamma$, G is the ln_gamma output of STATA.

Parameters: scale (lambda: λ), shape (gamma: γ)

Including hazard ratio to loglogistic distribution:

The loglogistic distribution is not a proportional hazard model it's an accelerated failure time model. This means HR can't be applied to this distribution. But as sensitivity analysis in this model loglogistic distribution is used and HR was used in the following way:

$$S_{BSC}(t) = S_{AXI}(t)^{\frac{1}{HR}} = \left(\frac{1}{1 + \lambda * t^{\frac{1}{\gamma}}} \right)^{\frac{1}{HR}}$$

where $S_{BSC}(t)$ is the survival function of BSC arm, $S_{AXI}(t)$ is the survival function of axitinib arm.

Parameters of axitinib survival curve: scale (lambda: λ), shape (gamma: γ, $G = \ln \gamma$).

And HR is the hazard ratio of axitinib versus BSC.

The following section displays the full results of the parametric survival analysis:

Prior Cytokine – Overall survival

10.19.1 *Axitinib*

[redacted]

10.19.1.1 Weibull

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.19.1.2 Gompertz

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.19.1.3 Log-logistic

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.19.1.4 Lognormal

[redacted]

[redacted]

[redacted]

[redacted]

Prior sunitinib – Overall survival

10.19.2 *Axitinib*

10.19.2.1 Exponential

10.19.2.2 Weibull

[redacted]

10.19.2.3 Gompertz

[redacted]

[redacted]

10.19.2.4 Log logistic

[redacted]

10.19.2.5 Lognormal

[redacted]

[redacted]

Prior cytokine – Progression free survival

10.19.3 *Axitinib*

10.19.3.1 Weibull

[redacted]

10.19.3.2 Gompertz

[redacted]

[redacted]

10.19.3.3 Log logistic

[redacted]

10.19.3.4 Lognormal

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Prior sunitinib – Progression free survival

10.19.4 *Axitinib*

Weibull

[redacted]

10.19.4.1 Gompertz

[redacted]

[redacted]

[redacted]

[redacted]

10.19.4.2 Log logistic

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.19.4.3 Lognormal

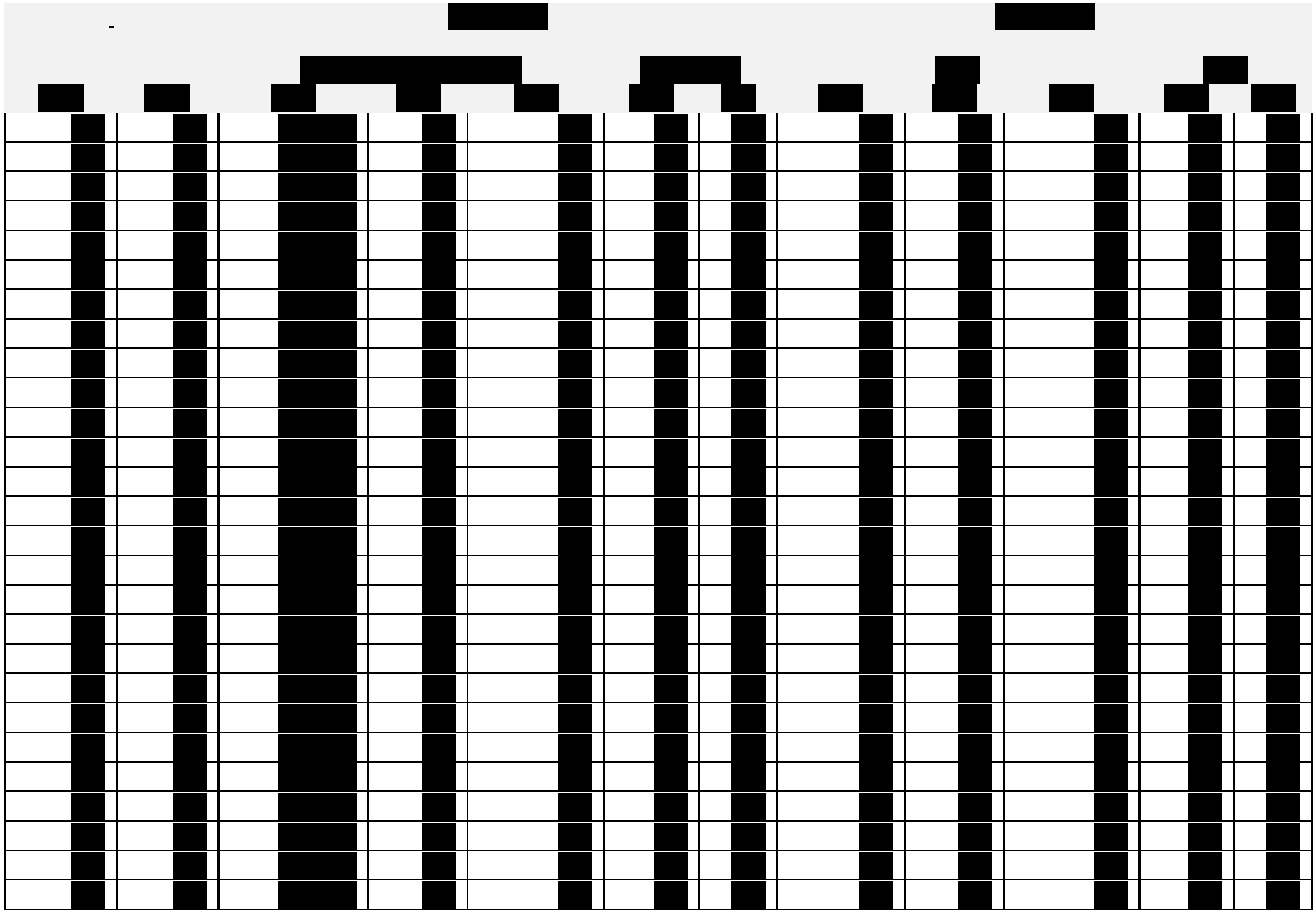
[redacted]

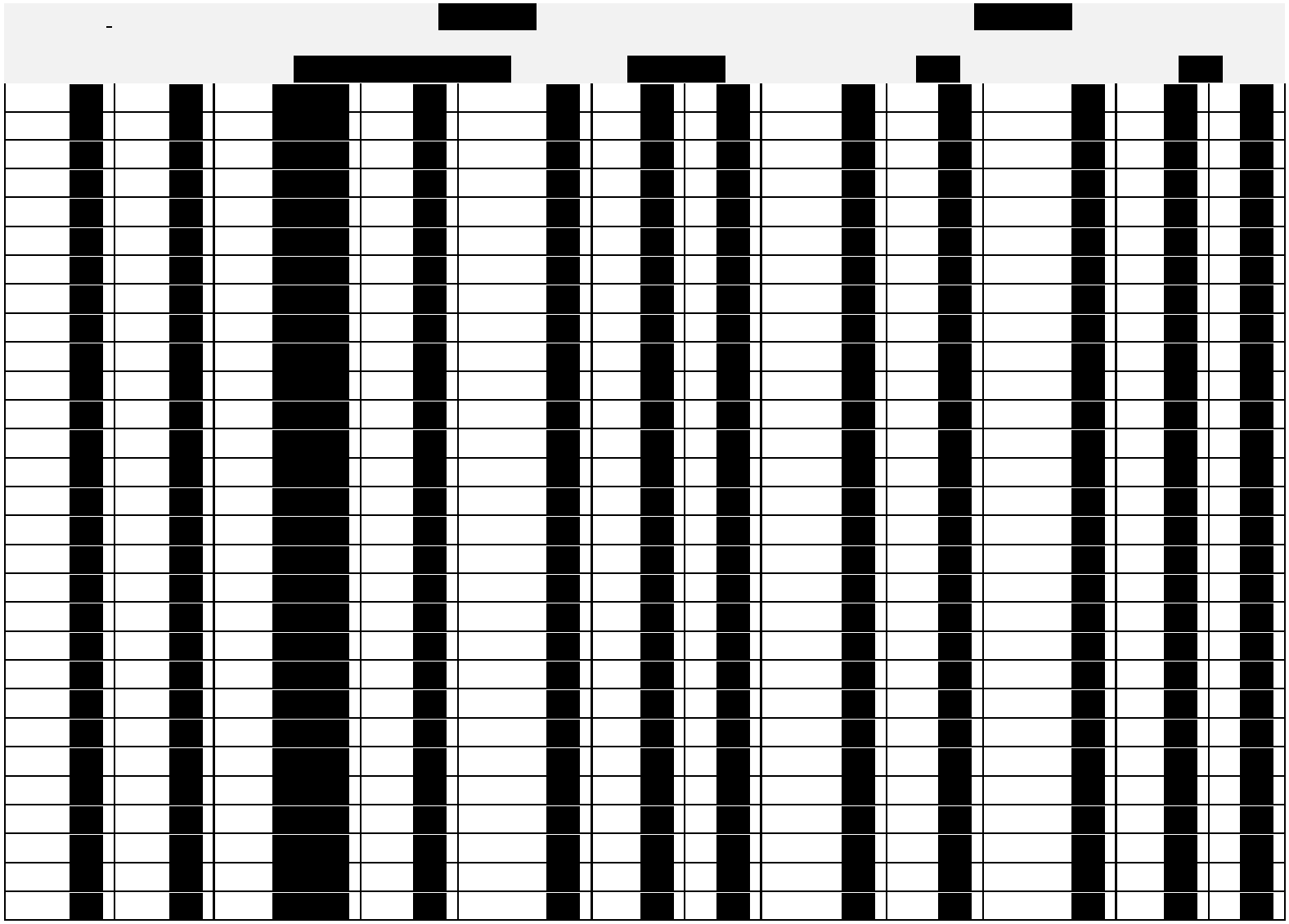
10.19.4.4 Model fit

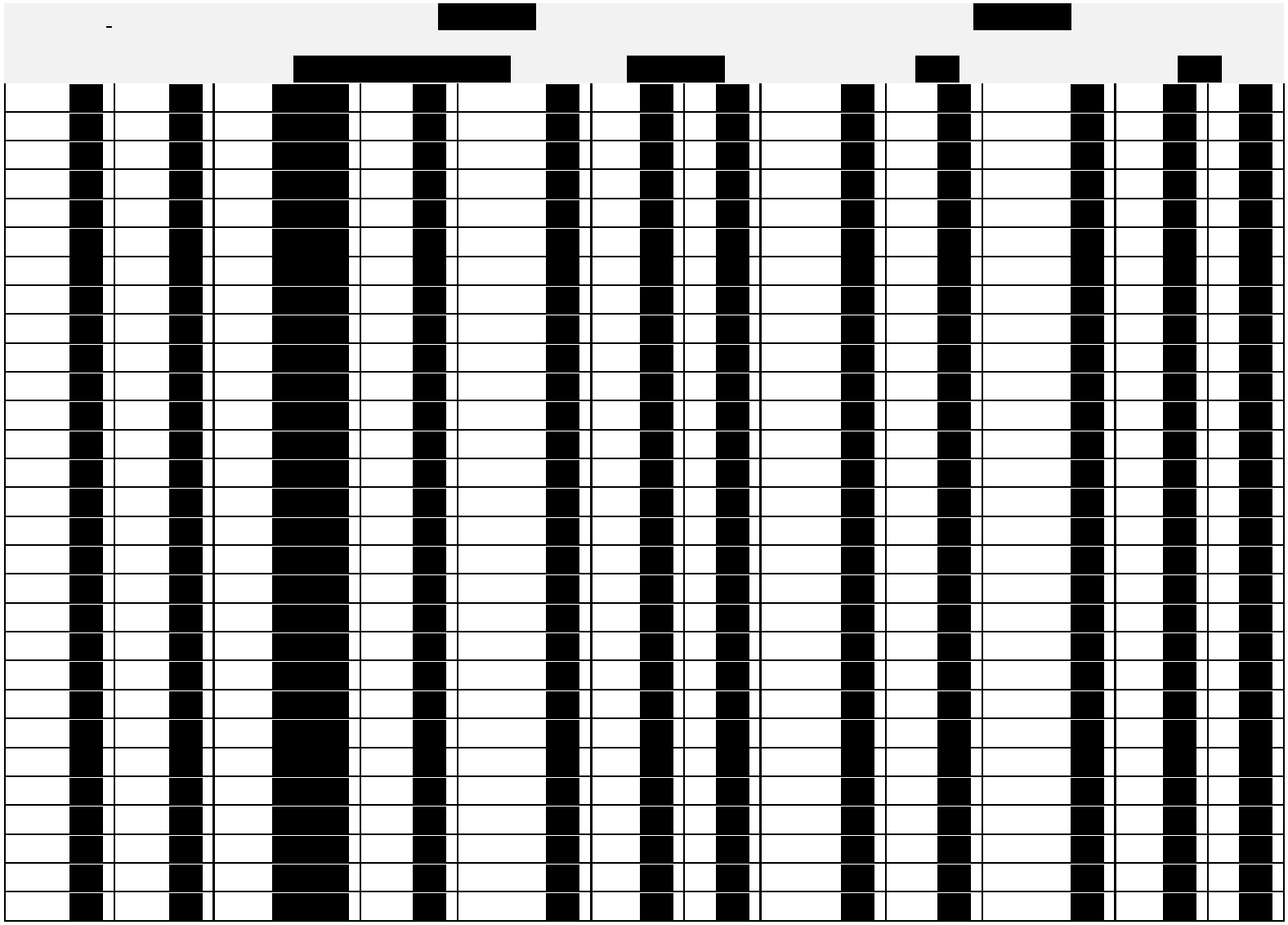
[redacted]

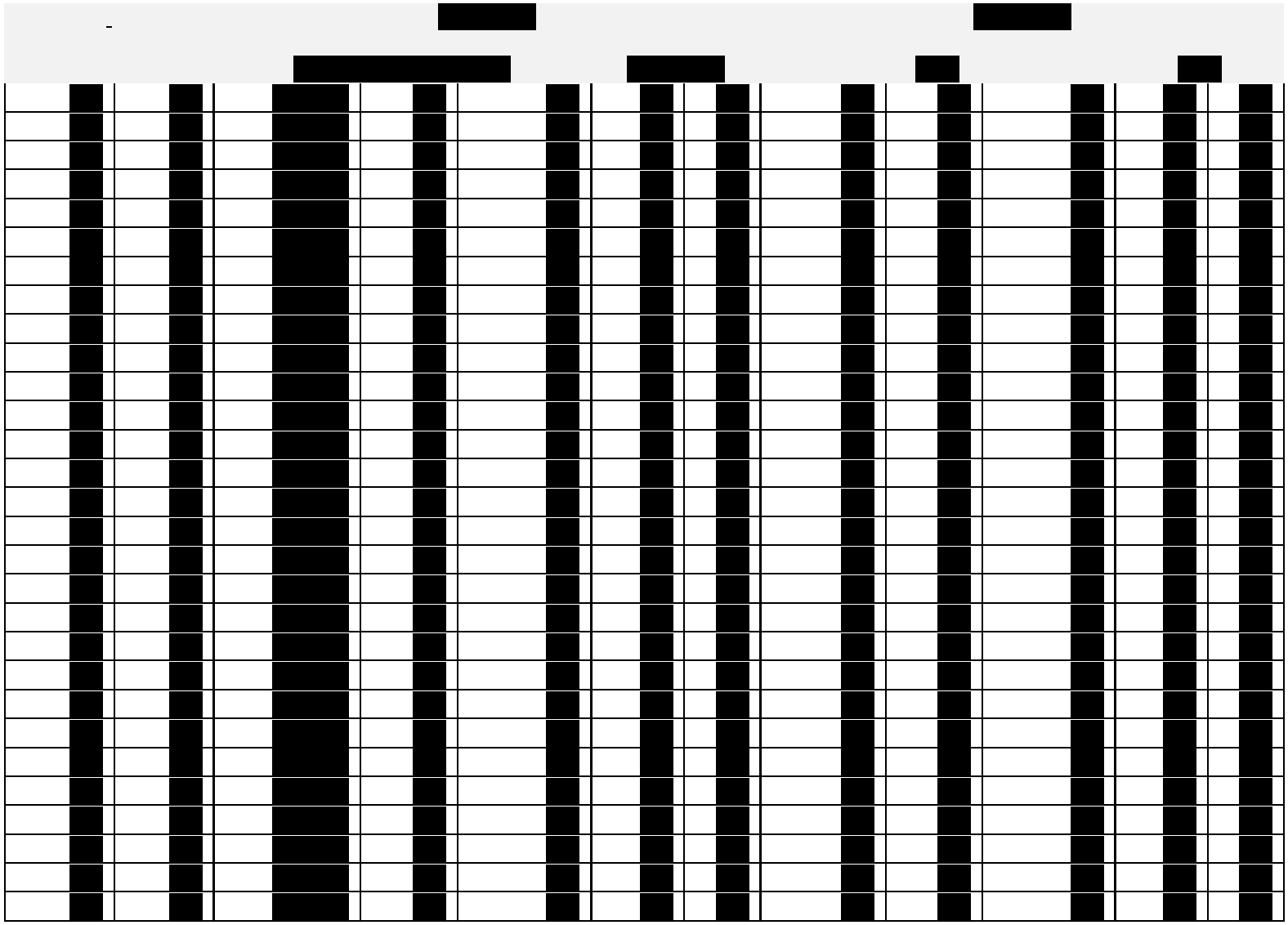
The following tables include Markov traces displaying the proportion of patients in each health state and QALYs accrued by cycle for the economic model for a 10-year period for a hypothetical cohort of 1,000 patients. These tables are aligned to the base case estimates for the sunitinib refractory and cytokine refractory populations. For the health state breakdown, figures displayed are undiscounted without a half-cycle correction applied. QALYs per state are discounted and have been adjusted with a half-cycle correction.

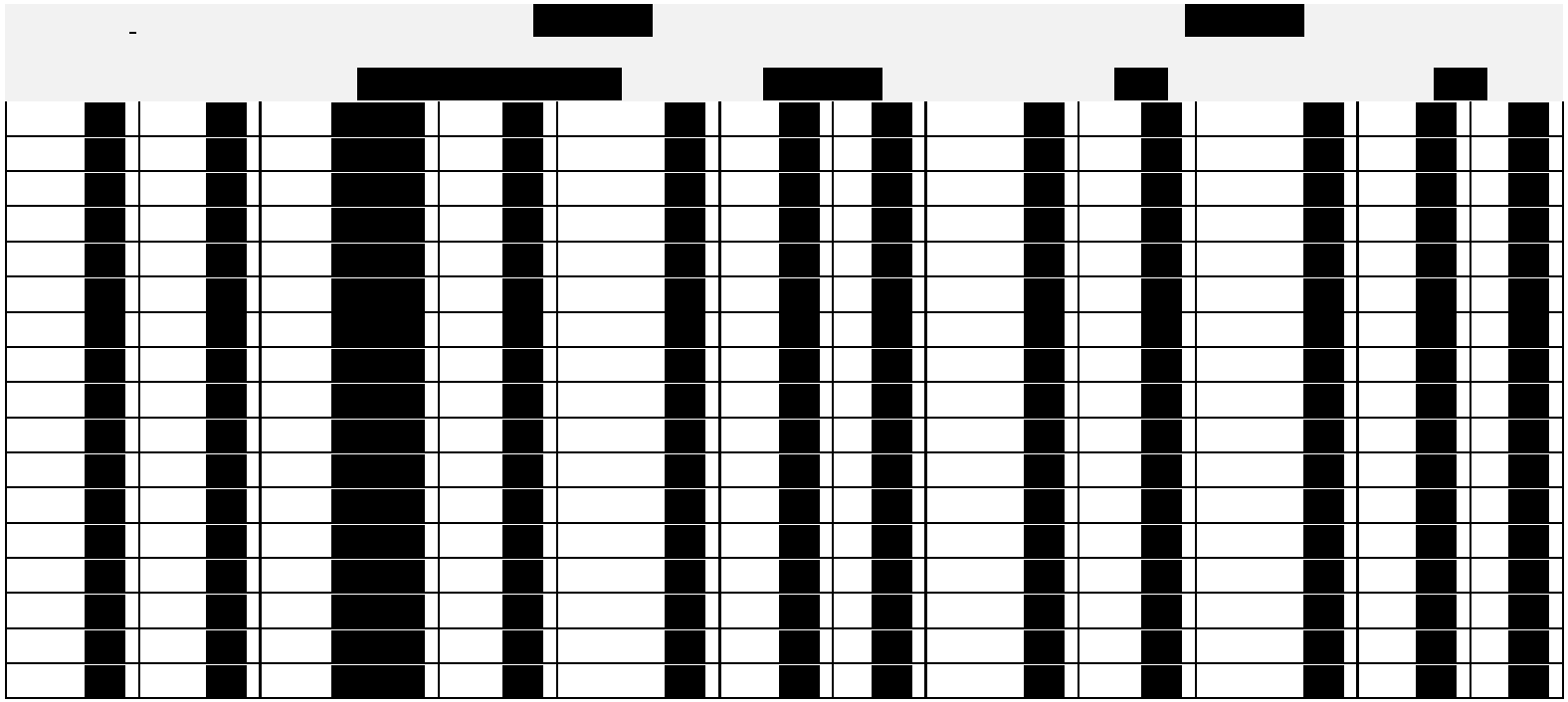
Prior Sunitinib:



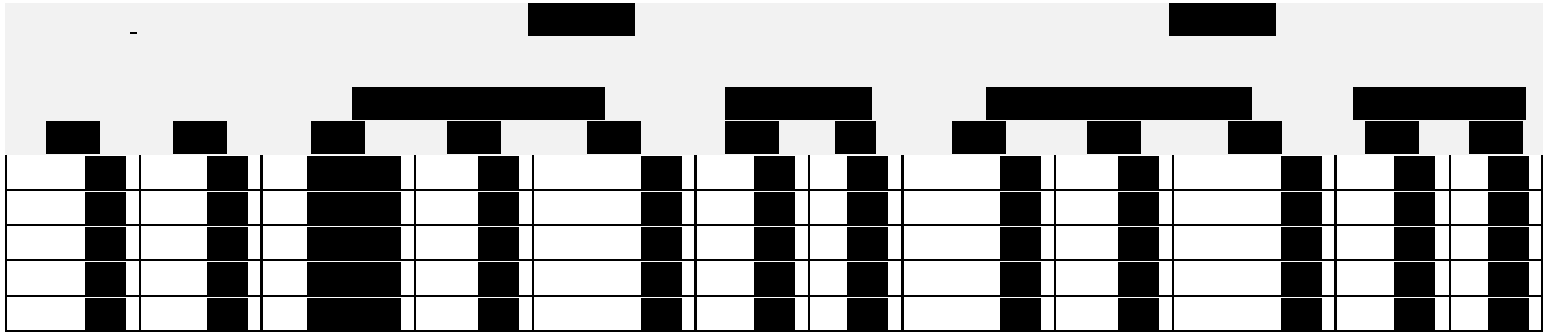


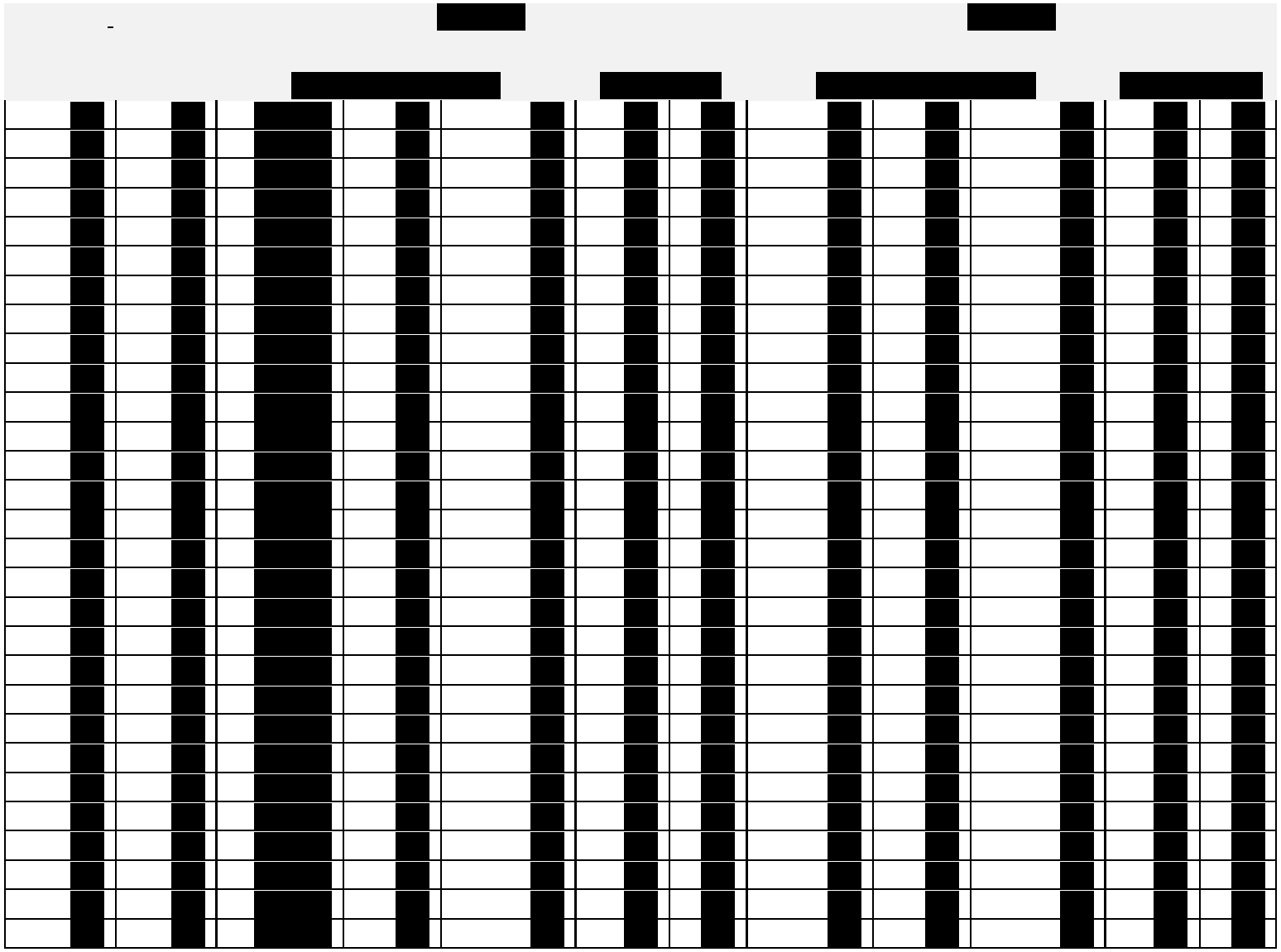


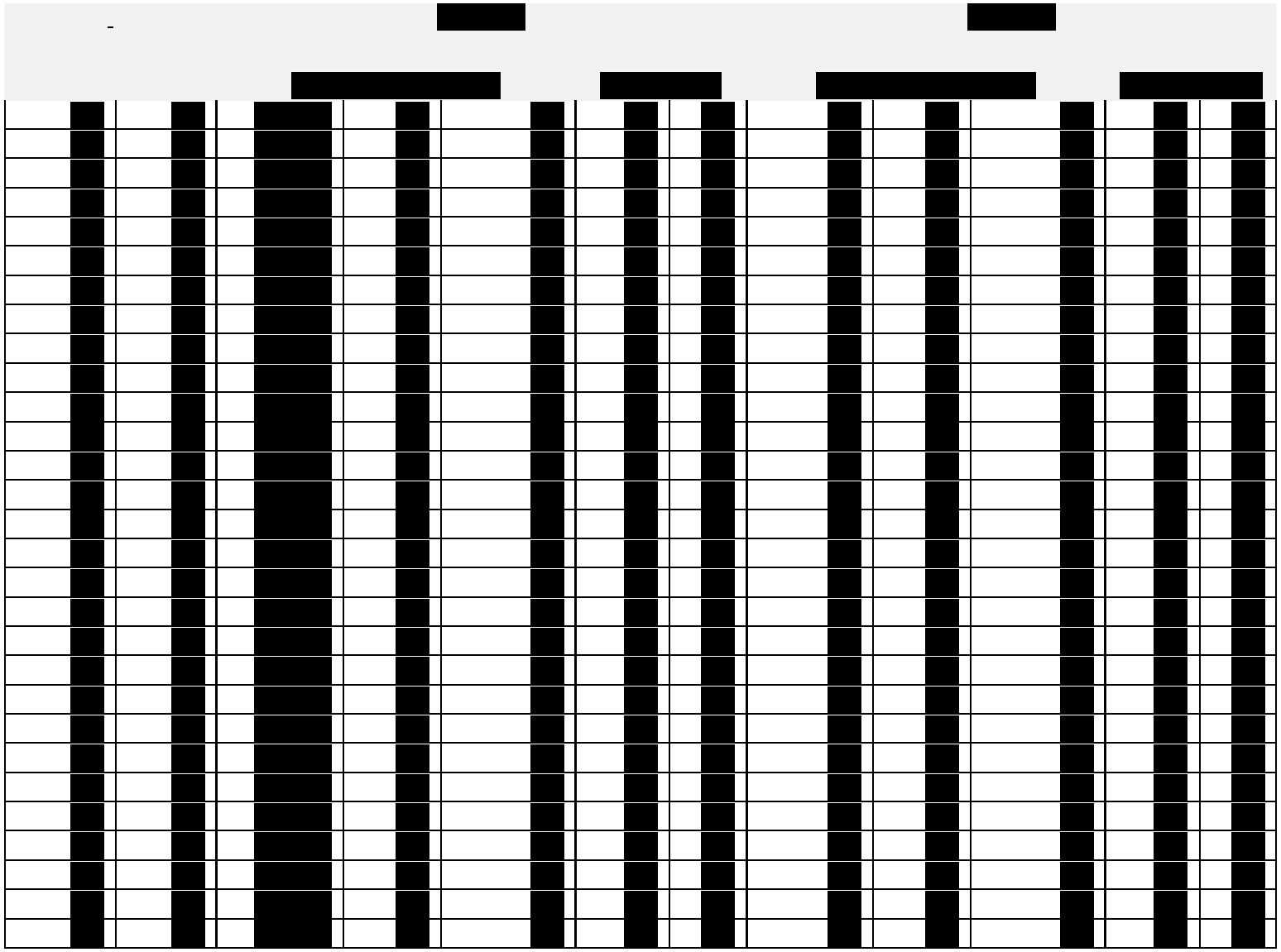


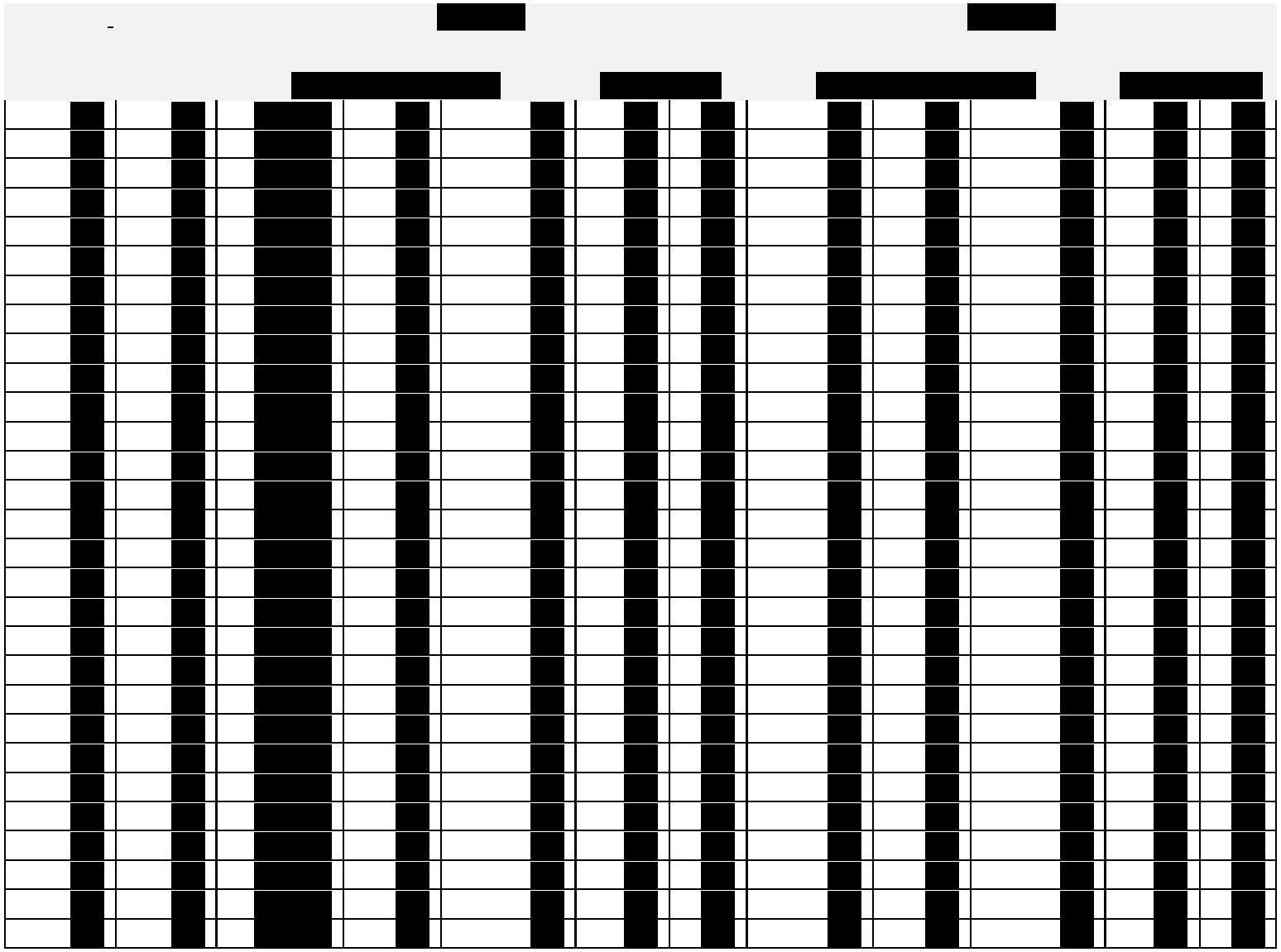


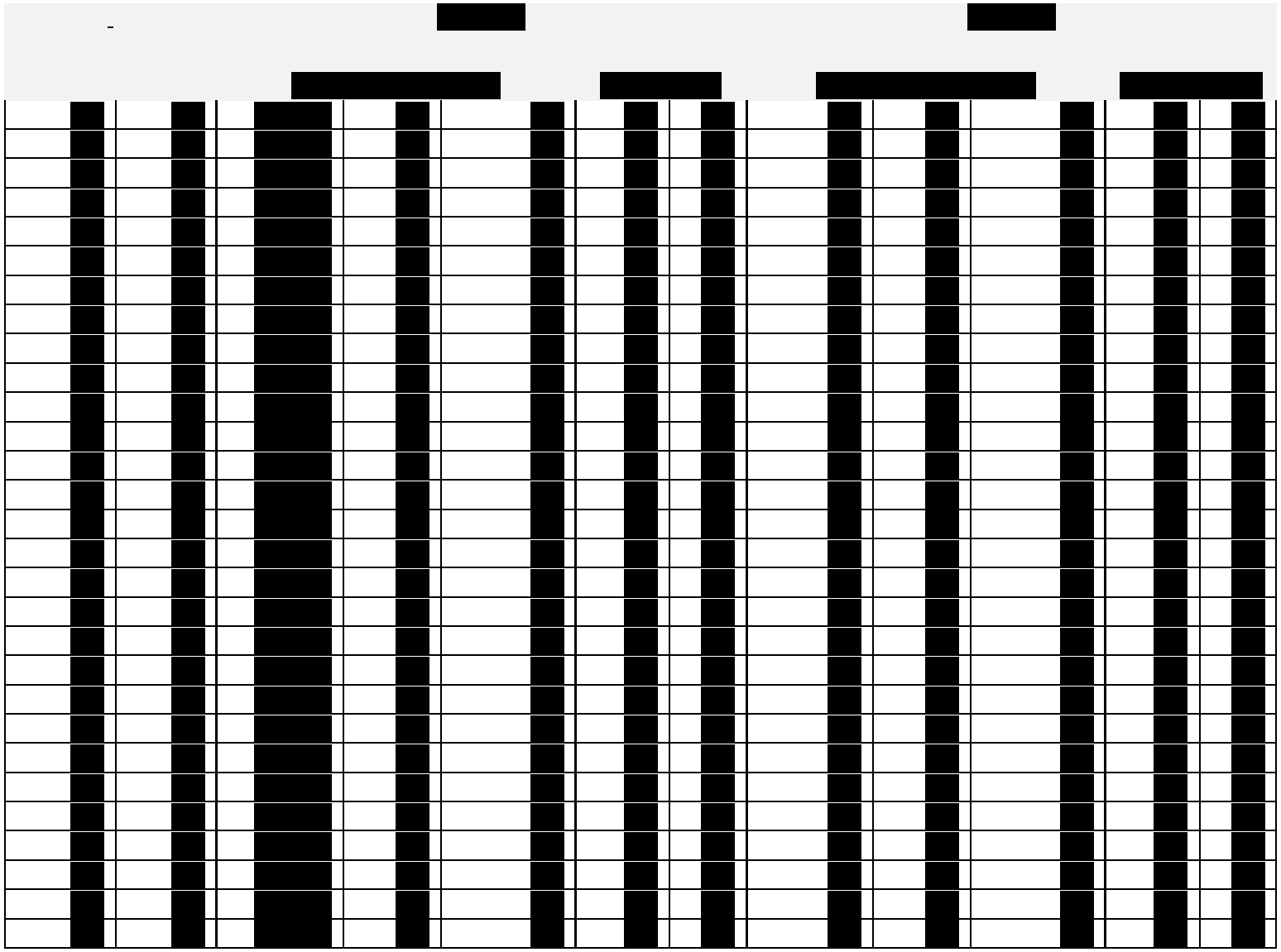
Prior Cytokine:

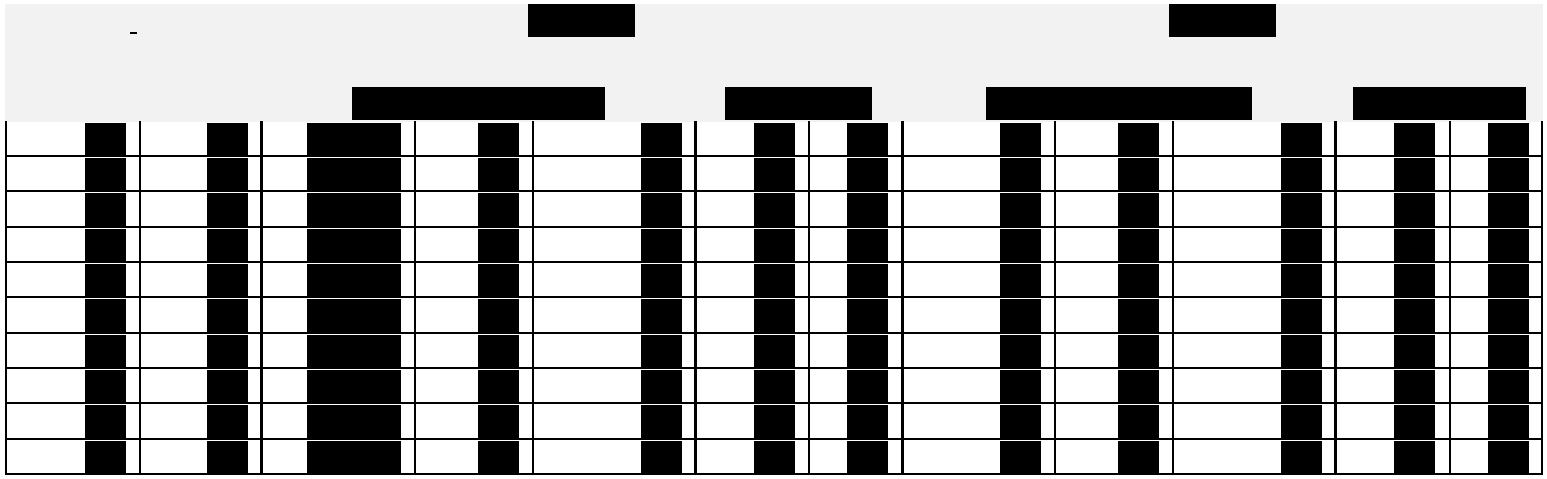












11 Related procedures for evidence submission

11.1Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the

agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.